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Unlocking a modular platform for bioacylation reactions enabling amide bond synthesis

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PURPOSE OF THE ABSTRACT

Acylation reactions, in particular amide bond formations, account for a vast number of transformations in organic synthesis. Undoubtedly, they are of utmost importance in medicinal chemistry and fine chemical synthesis to assemble complex molecules. Hence, there is a huge interest in the development of green methodologies that allow for the efficient formation of amides, whereas conventional approaches typically suffer from hazardous conditions, low atom economy as well as require toxic reagents. Enzyme-catalysed approaches that enable direct activation and functionalisation of carboxylic acids to amides are most sought after. Thioesters play a central and unique role as acyl carriers in enzyme catalysis due to their chemical properties as sufficiently stable, but highly reactive acyl building blocks. They are particularly relevant for the biochemistry of coenzyme A (CoA-SH) that functions as an essential cofactor for biocatalytic N-, O, and C-acylations. It is worth mentioning that a vast number of acyltransferases is available from natural sources, yet their applications are prohibited by restricted access to thioester substrates. Cognate coenzyme A (CoA-SH) ligases that are able to provide acyl-S-CoA substrates are typically rather specialised for their native carboxylic acid substrate and of limited use for biocatalysis . This dilemma demands for a more generic thioester generation and recycling system that can be applied in amide synthesis, for example. We found that the adenylation domain of a carboxylic acid reductase is able to function as a generic thioester synthetase, which can be utilised for the synthesis of acyl-S-CoA and other thioesters. This provides a widely applicable system for the in-situ-recycling of thioesters (Figure 1). Coupling the CoA-SH recycling system with different N-acyltransferases facilitates scalable and selective synthesis of a range of challenging amides in water at mild conditions. Exploiting this viable platform opens up manifold applications towards thioester-dependent, enzyme-catalysed C-N couplings and beyond. Recent developments of modular amide synthesis applying enzyme mining, engineering and cascade development in the context of pharmaceutical synthesis are being demonstrated.

FIGURES

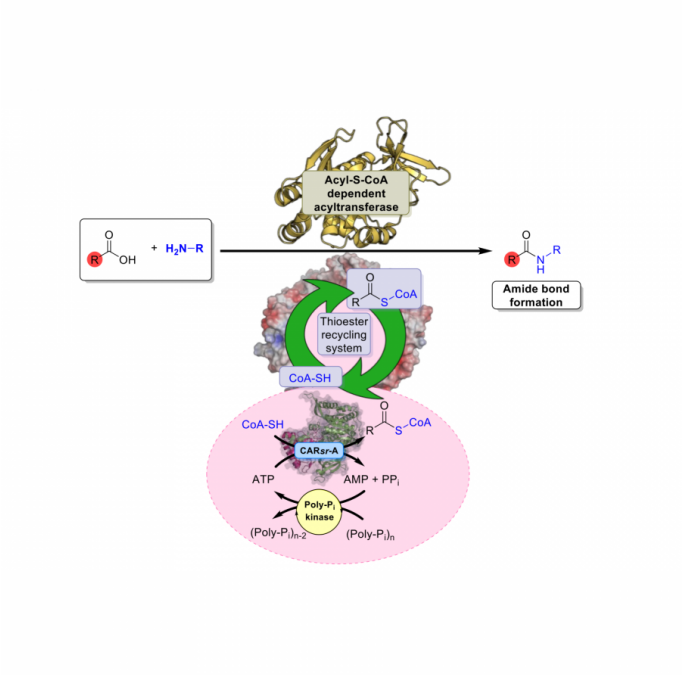

FIGURE 1

Figure 1

Adenylation domain of a carboxylic acid reductase functions as a versatile thioester synthetase providing a promiscuous in situ recycling system that can be exploited for amide synthesis.

FIGURE 2

KEYWORDS

Cascade | Cofactor regeneration | Carboxylic acid reductase | Amide synthesis

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