Exploring C-H Amination Methodology for the Preparation of Peptide Synthesis-Ready Enduracididine Derivatives

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Introduction

Antibiotic resistance poses a global health risk. This problem is compounded by the slow pace at which new antibiotics enter the market. Compared with other classes of drugs, antibiotics are costly to develop and offer poor financial returns; ergo, pharmaceutical companies are hesitant to invest in antibiotics.

January 2015 saw the much-celebrated discovery of teixobactin, a bacterial metabolite bearing potent antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Teixobactin is among a number of peptide-like antibiotics containing the rare amino acid enduracididine, which is produced in nature *via* enzymatic cyclization of arginine.[2] Multi-step syntheses of enduracididine have been achieved using glycine[3], proline[4], histidine[5] and aspartic acid-derived[6] precursors. Inspired by nature, we aim to develop a one-step synthetic route to enduracididine *via* oxidative cyclization of a commercially-available, protected arginine derivative.

Guanidino-containing molecules have been cyclized in high yields *via* C-H amination, a reaction shown to be most successful when performed with a trichloroethoxysulfonyl (Tces)-protected guanidino group and a rhodium-based catalyst, $Rh_2(esp)_2$.[7] We have explored applying this chemistry to arginine in order to design a more efficient method of synthesizing a precursor for peptide synthesis.

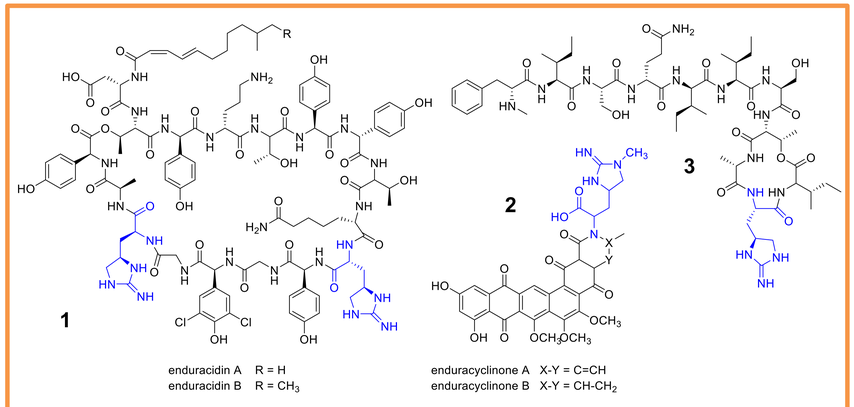
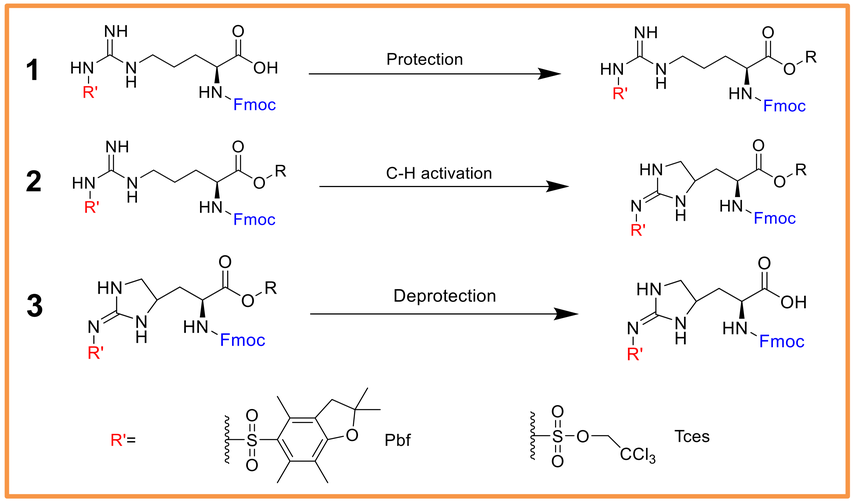
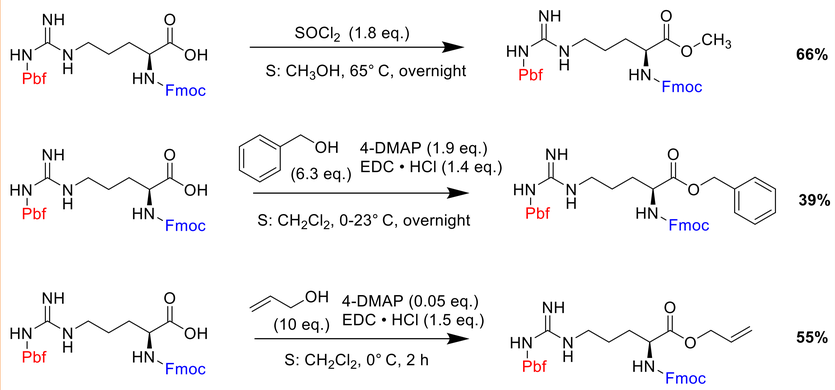


Figure 1. Molecular structures of enduracidin (1), enduracyclinone (2) and teixobactin (3), with enduracididine moieties highlighted.

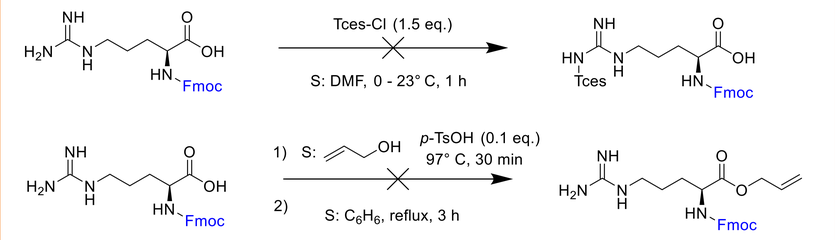
Project Goals



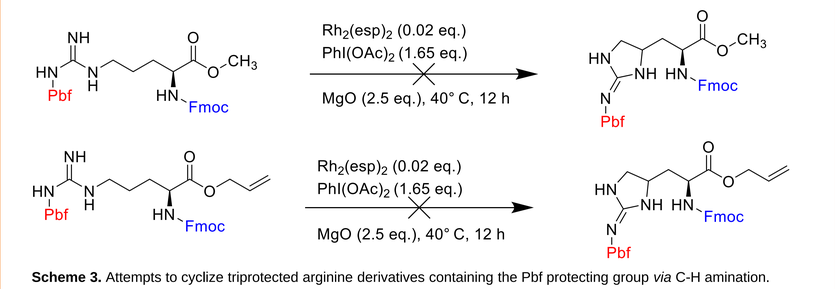
Results



Scheme 1. Syntheses of three distinct triprotected arginine derivatives from one diprotected starting material, Fmoc-Arg(Pbf)-OH.



Scheme 2. Attempts to protect the guanidino and carboxyl moieties of a monoprotected arginine derivative, Fmoc-Arg-OH.



Scheme 3. Attempts to cyclize triprotected arginine derivatives containing the Pbf protecting group *via* C-H amination.

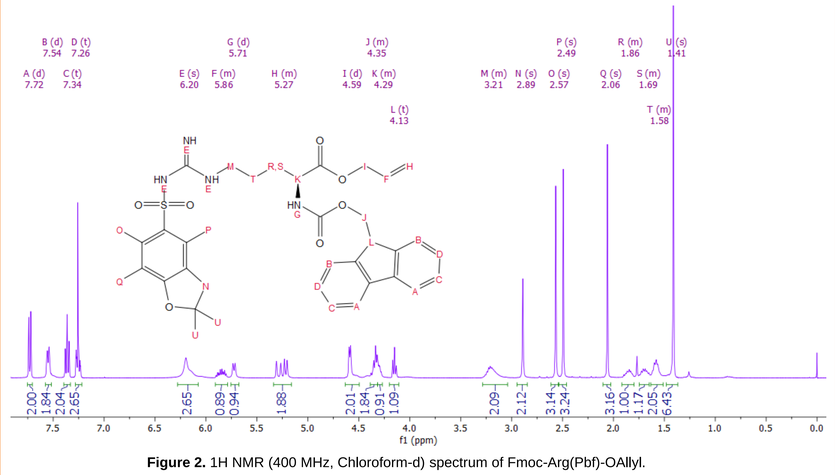


Figure 2. 1H NMR (400 MHz, Chloroform-d) spectrum of Fmoc-Arg(Pbf)-OAllyl.

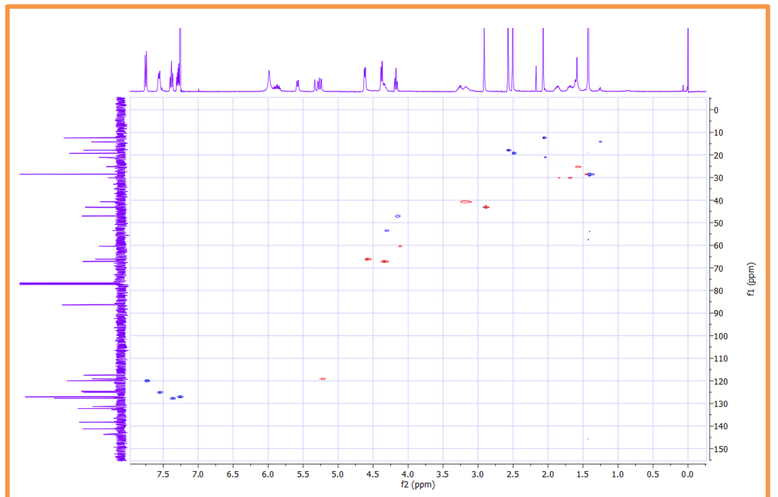


Figure 3. HSQC plot of Fmoc-Arg(Pbf)-OAllyl.

Discussion and Future

We have not conclusively demonstrated the successful ring closure of Pbf-containing substrates, suggesting that the Tces protecting group, as reported, is best suited for the oxidative cyclization of guanidine derivatives. We now point our attention to the introduction of the Tces group to the free guanidino moiety of a mono- or diprotected arginine derivative so that we may more accurately reproduce the ideal conditions needed for C-H amination.

Compared to other amino acids, arginine is difficult to handle due to its basic side chain. Organic reactions involving arginine are often complicated due to low solubility and may require the use of high-boiling point, polar aprotic solvents. These factors have kept us from successfully protecting Fmoc-Arg-OH *via* sulfonylation. Our efforts are now focused on synthesizing a more soluble arginine derivative containing a free guanidino group.

If we are able to demonstrate the efficient ring closure of arginine, we will then look to selectively liberate the carboxyl moiety of this amino acid so that it may be incorporated in solid-phase peptide synthesis.

Acknowledgements

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