Two-Step Synthesis Of Properly Protected and Activated Unnatural Amino Acid For Peptide Synthesis

Tech ID: 34533 / UC Case 2025-374-0

BACKGROUND

Unnatural amino acids (UAAs) or non-canonical amino acids (ncAAs) represent a multi-billion-dollar market, and they have been applied broadly in protein engineering, medicinal chemistry and drug discovery, diagnostics and biosensors, and catalysis science. Although enzymatic and chemoenzymatic synthesis offer efficient and highly stereoselective access to UAAs, they have significant shortcomings: these processes often require time-consuming and labor-intensive engineering, the reaction types are limited and the reaction conditions must be mild, the complexity of enzyme production at scale can be costly, and it is challenging to produce D-amino acids. As an alternative to an enzymatic approach, chemical synthesis avoids these issues, but it requires multiple steps, proper protection of amine and carboxylic acid groups, and may only produce moderate stereoselectivities and reaction yields. There is a need for an efficient chemical synthesis that is succinct, highly enantioselective, of broad reaction scope, readily forms either D- and L-amino acids or their equivalents, requires minimal functional group manipulations, and is amenable to direct peptide synthesis without carboxylic acid activation and with little or no epimerization.

DESCRIPTION

Researchers at the University of California, Santa Barbara have developed an efficient and highly enantio-selective two-step chemical method for synthesizing protected UAAs optimized for direct peptide synthesis. This novel technology enables the synthesis of UAAs featuring proper N-protection and mildly activated carboxylic acid moiety through a succinct two-step chemical process from readily accessible terminal alkynes. The amino acids produced typically exhibit over an enantiomeric excess of over 95%, which can be subsequently crystallized into enantiopure materials. The resulting UAAs can be employed directly for peptide bond formation in solution or solid-phase synthesis, eliminating the need for additional carboxylic acid activation steps and minimizing epimerization. The N-protecting group is stable to basic conditions and HOAc, is orthogonal to Fmoc/Alloc protecting group, and can be readily removed under acidic conditions without affecting N-Boc and trityl groups. This method offers a broad reaction scope, accommodating various functional groups, and can produce both D- and L-amino acid equivalents efficiently.

ADVANTAGES

- Cost-effective and efficient chemical alternative to enzymatic synthesis

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OTHER INFORMATION

KEYWORDS

amino acid, peptide, unnatural amino acids, non-canonical amino acids, sythesis, enzymatic synthesis, peptide synthesis

CATEGORIZED AS

- **Medical**
  - Other

RELATED CASES

2025-374-0

- Only two synthetic steps with high overall yields from readily accessible and often commercially available terminal alkynes
- Highly enantioselective (≥95% enantiomeric excess)
- Produces both D- and L-amino acids or equivalents
- Broad reaction scope supporting diverse functional groups at the AA side chain.
- Minimal functional group manipulation required before peptide coupling
- Directly amenable to peptide synthesis without additional carboxylic acid activation
- Suitable for rapid peptide synthesis (<10 min) under microwave heating and without epimerization

APPLICATIONS

- Peptide therapeutics
- Protein engineering and modification
- Medicinal chemistry and drug discovery
- Automated and manual peptide synthesis
- Diagnostics and biosensor development
- Catalysis science and chemical biology research
- Custom synthesis of unnatural amino acids for research and commercial use

PATENT STATUS

Patent Pending

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Highly Efficient Glycosylation Chemistry that Enables Automatic Carbohydrate Synthesis
- Sn2 Glycosylation Suitable For Automated Glycan Synthesis

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