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Highly Sterically Hindered Peptide Bond Formation between α,α-Disubstituted α-Amino Acids and *N*-Alkyl Cysteines Using α,α-Disubstituted α-Amidonitrile

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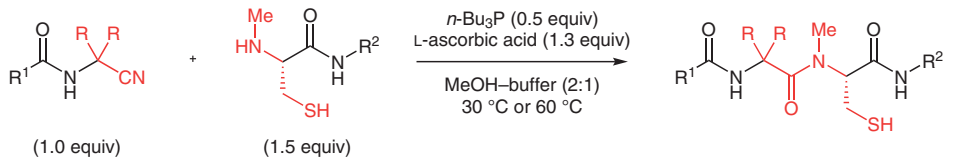
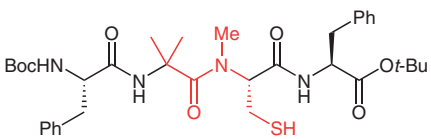
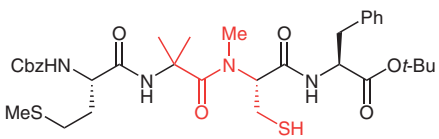
Synthesis of Peptides with the Formation of Highly Sterically Hindered Peptide Bonds



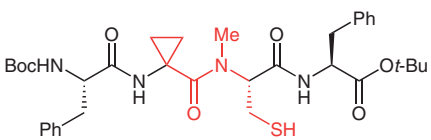
(1.0 equiv) (1.5 equiv)



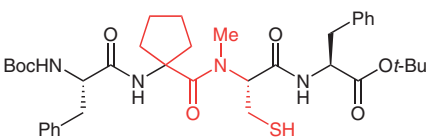
30 °C, 72 h, 87% yield



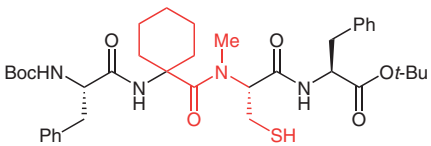
30 °C, 36 h, 81% yield



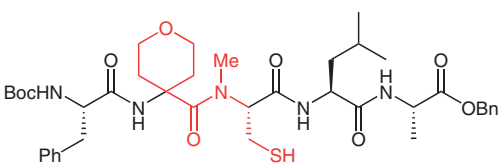
30 °C, 20.5 h, 85% yield



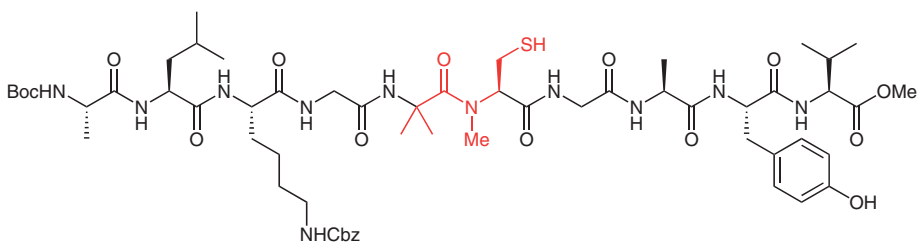
60 °C, 16 h, 85% yield



60 °C, 36 h, 79% yield



60 °C, 22 h, 78% yield



30 °C, 48 h, 77% yield[a]

[a]HCl•*N*-methyl cystenyl pentapeptide was used and $NaHCO_3$ (1.5 equiv) was added.

Significance: The introduction of unnatural amino acids, such as α,α-disubstituted α-amino acids, into peptide backbones is important in drug discovery and medicinal chemistry. The authors have developed a synthetic method for forming such highly hindered peptide bonds from α,α-disubstituted α-amidonitriles and *N*-alkylcysteines.

Comment: The method produced hindered peptide bonds in good yields. The reaction of α,α-disubstituted α-amidonitriles with *N*-alkylcysteines proceeds in the absence of a coupling reagent.

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Peptide Chemistry

Key words
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steric hindrance
alkylcysteines
amidonitriles

Synfact of the Month