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

**Significance:** The introduction of unnatural amino acids, such as \(\alpha,\alpha\)-disubstituted \(\alpha\)-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 \(\alpha,\alpha\)-disubstituted \(\alpha\)-amidonitriles and \(N\)-alkyl cysteines.

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

\[ \text{MeOH-buffer (2:1)} \]
\[ 30^\circ\text{C or 60^\circ C} \]
\[ n\text{-Bu}_3\text{P (0.5 equiv)} \]
\[ \text{L-ascorbic acid (1.3 equiv)} \]
\[ (1.0\text{ equiv}) \]
\[ (1.5\text{ equiv}) \]

**Key words**

- hindered peptide bonds
- steric hindrance
- alkylcysteines
- amidonitriles

**SYNFACTS Contributors:** Hisashi Yamamoto, An Wu

**SYNFACTS** 01092022, 18(09), 1043 Published online: 18.08.2022

DOI: 10.1055/s-0041-1738552; Reg-No.: H07022SF

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Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany