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Epimerization-Free C-Term Activation of Peptide Fragments by Ball Milling
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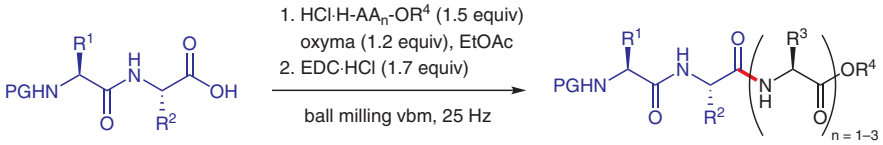
Ball-Milling Strategy for Epimerization-Free Peptide Synthesis



Product	time (min)	isolated yield (%)	de (%)
Z-Ala-Phg-Phe-OMe	20	89	>99
Z-Ala-D-Phg-Phe-OMe	20	92	>99
Z-Ala-Cys(Bn)-Ala-OMe	30	98	>99
Z-Ala-Cys(Bn)-Phe-OMe	20	94	>99
Z-Phe-Val-Cys(Bn)-OMe	30	98[a]	>99
Z-Phe-D-Val-Cys(Bn)-OMe	30	97	>99
Z-Phe-Val-Ser(*t*-Bu)-O*t*-Bu	30	97[a]	>99
Z-Phe-D-Val-Ser(*t*-Bu)-O*t*-Bu	20	97	>99
Boc-Trp-Phe-Glu(Bn)-OBn	15	92	>99
Boc-Trp-Phe-Gly-OBn	10	84	>99
Boc-Trp-D-Phe-Gly-OBn	10	95	>99
Z-Phe-Val-Leu-Leu-OBn	25	95[b]	>99
Z-Phe-Val-Leu-Leu-Leu-OBn	30	93[b,c]	>99
Z-Phe-D-Val-Leu-Leu-Leu-OBn	30	91[b,c]	99

[a] 1.2 Equiv of ECD·HCl was used. [b] 1.0 Equiv of HCl·H-AA$_n$-OR was used. [c] 2.2 Equiv of EDC·HCl, η (EtOAc) = 0.9 µL/mg and total mass = 267 mg.

Significance: Because of the large demand for peptides in various fields, chemists are actively searching for highly efficient and epimerization-free methods for peptide synthesis. The authors have developed a method involving ball milling for synthesizing peptides in high yields and with minimal epimerization.

Comment: The developed ball-milling strategy for coupling in which peptide fragments containing highly epimerization-prone and hindered amino acids at the C-terminus actively participate in the reaction to afford the desired peptides in high yields with excellent purity. This method requires a very small amount of solvent.

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Peptide Chemistry

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Synfact of the Month