A general method for preparation of *N*-Boc-protected or *N*-Fmoc-protected α,β-didehydropeptide building blocks and their use in the solid-phase peptide synthesis.

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Artykuł

Streszczenie

N-(*tert*-butyloxycarbonyl) or *N*-(9-fluorenylmethoxycarbonyl) dipeptides with C-terminal (*Z*)-α,β-didehydrophenylalanine (Δ^{Z}Phe), (*Z*)-α,β-didehydrotyrosine (Δ^{Z}Tyr), (*Z*)-α,β-didehydrotryptophan (Δ^{Z}Trp), (*Z*)-α,β-didehydromethionine (Δ^{Z}Met), (*Z*)-α,β-didehydroleucine (Δ^{Z}Leu), and (*Z*/*E*)-α,β-didehydroisoleucine ($\Delta^{Z/E}$Ile) were synthesised from their saturated analogues via oxidation of intermediate 2,5-disubstituted-oxazol-5-(4*H*)-ones (also known as azlactones) with pyridinium tribromide followed by opening of the produced unsaturated oxazol-5-(4*H*)-one derivatives in organic-aqueous solution with a catalytic amount of trifluoroacetic acid or by a basic hydrolysis. In all cases, a very strong preference for *Z* isomers of α,β-didehydro-α-amino acid residues was observed except of the ΔIle, which was obtained as the equimolar mixture of *Z* and *E* isomers. Reasons for the (*Z*)-stereoselectivity and the increased stability of the aromatic α,β-didehydro-α-amino acid residue oxazol-5-(4*H*)-ones over the corresponding aliphatic ones are also discussed. It is the first use of such a procedure to synthesise peptides with the C-terminal unsaturated residues and a peptide with 2 consecutive ΔPhe residues. This approach is very effective especially in the synthesis of peptides with aliphatic α,β-didehydro-α-amino acid residues that are difficult to obtain by other methods. It allowed the first synthesis of the ΔMet residue. It is also more cost-effective and less laborious than other synthesis protocols. The dipeptide building blocks obtained were used in the solid-phase synthesis of model peptides on a polystyrene-based solid support. Peptides containing aromatic α,β-didehydro-α-amino acid residues were obtained with PyBOP or TBTU as a coupling agent with good yields and purities. In the case of aliphatic α,β-didehydro-α-amino acid residues, a good efficiency was achieved only with DPPA as a coupling agent.