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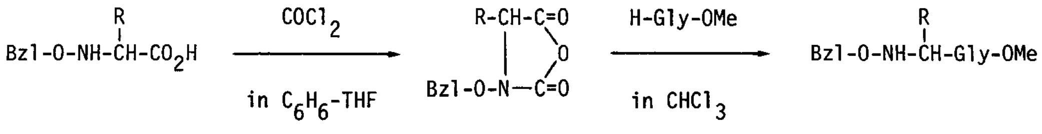
N-HYDROXYPEPTIDES. I. PREPARATION OF N-BENZYLOXY-α-AMINO ACID ANHYDRIDES AND THEIR USE IN PEPTIDE SYNTHESIS

Masayasu Akiyama,* Masayoshi Hasegawa, Haruyuki Takeuchi, and Kazuyuki Shimizu
Department of Industrial Chemistry, Tokyo University of Agriculture
and Technology, Koganei, Tokyo 184, Japan

Summary: N-Benzyloxy-DL-α-amino acids are transformed with phosgen to N-benzyloxy-DL-α-amino acid anhydrides which react smoothly with the amino component of peptides to give the corresponding N-benzyloxypeptides.

Synthesis of peptide analogs which have the N-hydroxyamide function in their sequence is of interest in relation to naturally occurring hydroxamic derivatives.[1] Current efforts for these analogs are rather limited to several separate instances,[1,2] although some general syntheses of O-protected N-hydroxyamino acids and their derivatives have been carried out.[3,4] We wish to report here on a general method for synthesis of these peptide analogs.

The method consists in the preparation of the N-carboxyamino acid anhydrides (NCAs) of O-protected N-hydroxy-α-amino acids and their use for reactions with the amino component of peptides. The benzyl group was chosen for protection of the N-hydroxyl group, because its easy deprotection has been demonstrated in several cases.[4] Despite the low basicity of the oxyamino group,[4] pure NCAs (2) of N-benzyloxy-DL-α-amino acids (1) were obtained in good yields: To a suspension of the amino acid (1) (0.05 mol) in benzene-THF (120 ml), was introduced phosgen generated from trichloromethyl chloroformate (0.125 mol) and the mixture was stirred at 40°C for 2 hr. Solvents were evaporated to give an oily residue, which usually crystallized by treatment with hexane-THF. It was recrystallized from hexane-THF. The results of the NCA preparation are as follows: 2, R, yield, mp°C: 2a, H, 46%, 63.5-64°; 2b, Me, 68%, 71-72°; 2c, Et, 66%, 65.5-66°; 2d, Pr^i, 52%, 50.5-51°; 2e, Bu^i, 54%, oil; 2f, Bzl, 69%, 147.5-148°.[5]



1a-f 2a-f 3a-f

An equimolar reaction of the NCA (2) with methyl glycinate proceeded smoothly to produce the corresponding dipeptide, Bzl-O-NH-CH(R)-CO-Gly-OMe (3): To a cooled (0°C) stirred mixture of methyl glycinate hydrochloride (0.01 mol) and triethylamine (0.01 mol) in $CHCl_3$ (50 ml) was added the NCA (2) (0.01 mol) in $CHCl_3$ (20 ml). The stirred mixture was kept at 0°C for 2 hr and then at ambient temperaure for 2 days. After the usual work-up, the dipeptide (3) was obtained as a hydrochloride salt with HCl-dioxane, and it was recrystallized from methanol-ether. The results are as follows: 3, yield, mp°C: 3a, 100%, 124-126°; 3b, 89%, 165-166°; 3c, 95%, 172-173°; 3d, 91%, 183-184°; 3e, 95%, 138-139°; 3f, 92%, 168-169°.[5] As seen in these results, the yields are excellent in most cases. Clean reactions in this stepwise method are attributable to the slowness of the reaction between the newly formed free benzyloxyamino group and a second molecule of the NCA.

For further elongation of the N-benzyloxydipeptides, routine coupling methods of peptide synthesis may be used in combination with the present NCA procedure. Thus, by a mixed anhydride method using isobutyl chloroformate and triethylamine, Boc-glycine and H-N(OBzl)-DL-Ala-Gly-NHPh (3g)[6] gave Boc-Gly-N(OBzl)-DL-Ala-Gly-NHPh (4) of mp 121-122°C in 74% yield. The tripeptide (4), after deprotection of the Boc-group, was coupled with 2b in $CHCl_3$ at room temperature to give a tetrapeptide, H-N(OBzl)-DL-Ala-Gly-N(OBzl)-DL-Ala-Gly-NHPh (5) of mp 123-124°C in 91% yield.[5]

The present method seems to be particularly suitable for the synthesis of peptides having an alternate amide and N-hydroxyamide sequence in the chain. Although the products obtained here are racemic, the method will be applicable to the synthesis of optically active compounds, and studies in this direction are now in progress.

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References and Notes

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5. Satisfactory elemental analyses were obtained for these new compounds.
6. By the reaction of 2b with H-Gly-NHPh, 3g was obtained in 72% yield, mp 139-140°C.

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