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PREPARATION OF SUBSTITUTED N-CARBOXYMETHYL DIPEPTIDES

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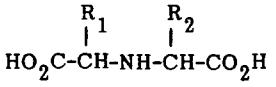
Abstract: The use of dipeptides as amine components in a Strecker reaction with aldehydes provides a facile route to substituted N-carboxymethyl dipeptides.

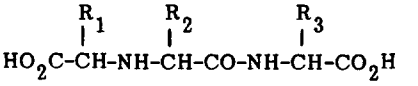
Recently a variety of modified amino acids have been studied as possible antimetabolites or enzyme inhibitors. One such type of unusual amino acid, represented by structure 1 occurs in nature and has been the subject of a systematic investigation.[1] Recently these N-carboxymethyl amino acids have been incorporated into peptides.[2] Although substituted N-carboxymethyl amino acids (2) have not been reported, recently a series of substituted N-carboxymethyl dipeptides (3) has been prepared and demonstrated to be active as inhibitors of angiotensin converting enzyme.[3] This, coupled with the possibility that 3 might function as inhibitors of other enzymes,[4] makes facile routes for their preparation desirable.

Although substituted N-carboxymethyl dipeptides have been prepared from the parent dipeptides by alkylation with an α-haloester, or reductive alkylation with an α-ketoester,[3] often these starting materials are available only by multistep syntheses, especially when they contain additional functional groups. We now report a facile route to 3 in which the dipeptide is used as the amine component in a Strecker reaction with an aldehyde (R_1-CHO).



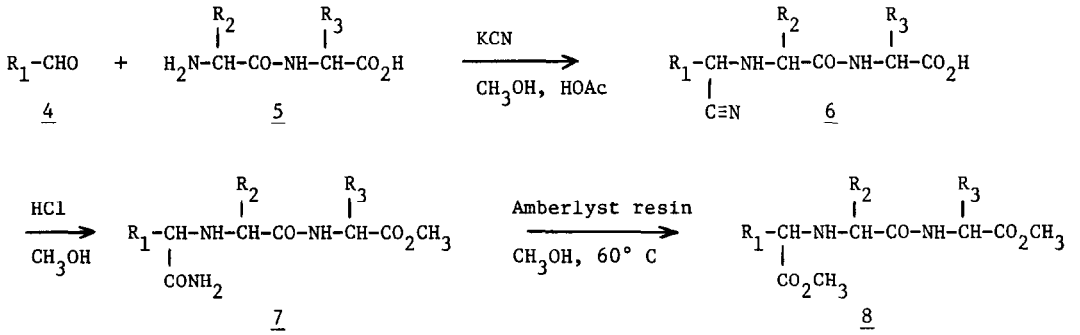
1 R_1 = H; R_2 = alkyl

2 R_1 = R_2 = alkyl



3

SCHEME 1



When aldehydes 4 were combined with dipeptides 5 and potassium cyanide in methanol solution, slow but complete conversion to aminonitriles 6 was observed. The aminonitriles could be isolated in good yield by ion-exchange chromatography, but were conveniently used in the next step without purification. Since normal Strecker hydrolysis conditions (concentrated HCl at reflux) were expected to bring about the hydrolysis of the peptide bond, a milder procedure for the nitrile to ester conversion was required. Treatment of aminonitriles 6 with HCl-saturated methanol at 0°C led to rapid and complete conversion to amidoesters 7.[6] The acidic-resin promoted methanolysis of the amidoesters using Amberlyst 15 resin,[7] then provided the diesters 8, which were purified by column chromatography on silica gel.

Examples of the synthesis are shown in the Table. In all cases, diesters 8 were formed as mixtures (approximately 1:1) of diastereomers about the new asymmetric center, which were separable by silica gel chromatography. Diacids 3 were readily prepared from 8 by saponification (1N NaOH), followed by ion-exchange chromatography (DOWEX 50) using H_2O-pyr (25:1) as eluant.[11]

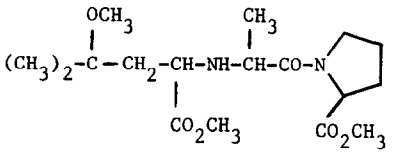
General Procedure:

The aldehyde (1.2 mmol) was added to a mixture of the dipeptide (1.0 mmol), potassium cyanide (1.2 mmol), and acetic acid (1.2 mmol) in methanol (3 ml). The flask was tightly capped and the mixture was stirred for 48 hours.[12] Additional methanol (3 ml) was added and the mixture was cooled (ice-bath) and saturated with anhydrous HCl. The flask was again stoppered and the cooled mixture was stirred for 4 hours. The mixture was evaporated to dryness, then slurried in methylene chloride as excess anhydrous ammonia was passed in. The mixture was immediately evaporated, slurried in ethyl acetate, filtered and the filtrate evaporated. To the resulting crude amidoester[6] were added Amberlyst 15 acid resin[7] (7 g) and methanol (20 ml) and the mixture was warmed at reflux with gentle stirring for 48 hours. The resin was collected in a small column and washed with methanol. Then the product was eluted with 2:1 CH_3OH-pyr and purified by silica gel chromatography.[8]

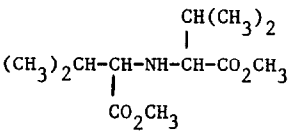
Table: Preparation of Diesters 8[8]

Aldehyde	Dipeptide[10]		Yield
$PhCH_2CH_2CHO$	Ala-Pro	(S,S)	59%
$(CH_3)_2CHCH_2CHO$	Ala-Pro		68
$(CH_3)_2C{=}CHCHO$	Ala-Pro		55[a]
$PhtN(CH_2)_3CHO$	Ala-Pro		60
$PhCONHCH_2CHO$	Ala-Pro		45
PhCHO	Val-Tyr	(S,S)	83
$PhCH_2CH_2CHO$	Leu-Phe	(S,S)	69
$(CH_3)_2CHCHO$	Ala-Phe	(S,S)	25
2-Naphthyl-CHO	Phe-Leu	(S,S)	81
$(CH_3)_2CHCHO$	Leu-OMe·HCl	(S)	59[b]

a) The product in this case had this structure:



b) In this reaction the amino acid hydrochloride was used and the acetic acid was omitted. The product had the following structure:



References:

1. T. Miyazawa, Bull. Chem. Soc. Jpn., 53, 2555 (1980) and references cited therein.
2. T. Miyazawa, ibid., 53, 3661 (1980).
3. A. A. Patchett, et al., Nature, 288, 280 (1980).
4. Inhibition of thermolysin by substituted N-carboxymethyl dipeptides has recently been reported.[5]
5. A. L. Maycock, D. M. DeSousa, L. G. Payne, J. ten Broeke, M. T. Wu, and A. A. Patchett, Biochem. Biophys. Res. Commun., 102, 963 (1981).

6. Amidoesters 7 were occasionally accompanied by small amounts (5-10%) of diesters 8, but attempts to increase the amount of 8 were unsuccessful.

7. W. J. Greenlee, and E. D. Thorsett, J. Org. Chem., 46, 5351 (1981). Amberlyst is a trademark of Rohm and Haas Co., Inc. The resin was purchased from Aldrich Chemical Co.

8. Diesters 8 were characterized by ir, proton nmr, and mass spectral analyses. Column chromatography was carried out by flash chromatography[9] or by MPLC on E. Merck Lobar (size b) silica gel columns.

9. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923 (1978).

10. Except for Ala-Pro, which elemental analysis showed to be a hemi-hydrate, the dipeptides (Sigma Chemical Co.) were assumed to be anhydrous.

11. For example, the diester 8 prepared from 3-phenylpropionaldehyde and Ala-Pro (Table, entry 1) yielded the N-carboxymethyl dipeptide in 85% yield.

12. For slightly-soluble dipeptides (e.g. Leu-Phe) the reaction time was lengthened. The formation of 6 is readily monitored by TLC on silica gel using $CHCl_3$-CH_3OH-H_2O-AcOH (85:30:5:1) as developer.

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