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Further Applications of the 4-(Methylthio)-phenyl Ester in Peptide Chemistry

Keyphrases ☐ 4-(Methylthio)phenyl ester—peptide synthesis ☐ *N*-Carbobenzoxy-L-prolylglycylglycine ethyl ester—synthesis ☐ Optical rotation—identity

Sir:

The synthesis of proline containing peptides usually proceeds without complication, however, the alkaline hydrolysis of such sequences are frequently accompanied by side reactions. The hydrolysis of *N*-carbobenzoxy-glycyl-L-proline methyl ester with 1 *N* NaOH can be conducted with practically no cleavage of the peptide bond (1, 2). However, in the case of *N*-carbobenzoxy-L-prolylglycine methyl ester, hydrolysis causes cleavage to the extent of 70% yielding *N*-carbobenzoxy-L-proline and glycine (2). It is also difficult to hydrolyze higher peptides containing the sequence prolylglycyl in satisfactory yields (3).

In order to overcome this difficulty inherent in the synthesis of such sequences we have found that the 4-(methylthio)phenyl (MTP) protective ester (4–7) because of its facile conversion to the activated 4-(methylsulfonyl)phenyl (MSO_2P) ester, to be particularly useful for extending the peptide chain. For this purpose the synthesis of *N*-carbobenzoxy-L-prolylglycylglycine ethyl ester (Eq. 1) is described

Z-Pro-Gly-Gly-OEt (Eq. 1)

The synthesis commenced with the condensation of *N*-carbobenzoxy-L-proline and glycine 4(methylthio)-phenyl ester hydrochloride (4) using dicyclohexylcarbodiimide and triethylamine to give *N*-carbobenzoxy-L-prolylglycine 4-(methylthio)-phenyl ester, m.p. 92°, $[\alpha]_D$ −60° (c 3.23 in dimethylformamide).

In order to extend the peptide chain it was necessary to convert this protective MTP ester to its activated MSO_2P counterpart. This was achieved by the use of *m*-chloroperoxybenzoic acid in dioxane (7) for 4 hr., to yield *N*-carbobenzoxy-L-prolylglycine 4-(methylsulfonyl)phenyl ester, m.p. 117°, $[\alpha]_D$ −45°, (c 8.8 in dimethylformamide). The peptide chain was then extended through this MSO_2P activated ester by reaction of the dipeptide with glycine ethyl ester hydrochloride in the presence of triethylamine to give *N*-carbobenzoxy-L-prolylglycylglycine ethyl ester (8) (Eq. 1) m.p. 122°, $[\alpha]_D^{25}$ −23° (c 1 in ethanol).

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[1] The elemental analysis of all compounds were within experimental tolerance.