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CARBOXAMIDOMETHYL ESTERS (CAM ESTERS) AS CARBOXYL PROTECTING GROUPS.

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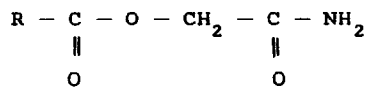
Summary : The carboxamidomethyl esters (CAM esters) are proposed for carboxyl protection in peptide synthesis. Amino acid CAM ester derivatives were easily prepared and showed good stability in the deblocking conditions of other common protecting groups used in peptide synthesis. The CAM esters were selectively and rapidly hydrolyzed in an alcaline medium.

The majority of carboxyl protecting groups[2] commonly used are cleaved by hydrogenolysis, acidolysis, alkaline hydrolysis, or treatment with metals. Recently, the fluorenyl methyl esters (Fm esters) were proposed[3-4]. They are gently removed by secondary amines and by hydrogenolysis.

As part of our program for developing a compatible set of new protecting groups for peptide synthesis, we report the preparation and uses of a new carboxyl protecting group, the CAM esters (CarboxAmidoMethyl Esters) which can be used in combination with Boc, Z and FMOC protecting groups.



CAM ester.

We have found CAM esters -to be inert to the functional groups of peptides and to their isolation procedures -to be removable quantitatively under very mild reaction conditions without affecting other protecting groups - to remain intact during the procedures used to remove other common protecting groups.

The preparation of CAM esters proceeds from readily available starting materials. N-protected amino acids are converted to their cesium salts, as described by Gisin[5]. These salts were allowed to react with commercially available α-chloro-acetamide (or α-iodo-acetamide) to yield the corresponding CAM esters. The yields were not optimized but in all cases sufficient for practical work. The CAM esters we synthesized were crystalline coumpounds (table I).

The CAM esters are not affected under peptide synthesis coupling conditions (DCC[6], active esters[7], BOP[8]). They are stable several hours in trifluoroacetic acid. They remain unchanged during hydrogenation using Pd/C 10% as catalyst (or $Pd/BaSO_4$ 10%). In the presence of cyclohexylamine (or TEA) in DMF, no cleavage of the CAM ester can be observed.

Table I :

Analytical data of amino acid CAM esters.

	Yield %	mp°C	$[\alpha]_D^{20}$
Boc-Gly-CAM	85	64-67	
Z-Gly-CAM	85	105-108	
Boc-L-Phe-CAM	75	113-116	-16 (2.95 EtOH)
Z-L-Phe-CAM	80	105-108	-24 (c 3.05 EtOH)
Boc-L-Ala-CAM	80	96-98	-27 (c 2.1 DMF)
Z-L-Ala-CAM	80	60-64	-13 (c 2.1 DMF)
Boc-L-Pro-CAM	70	78	-54 (c 2.05 EtOH)
Boc-L-Met-CAM	60	78-81	-29 (c 2.7 DMF)
Bz-L-Leu-CAM	75	129-132	- 7 (c 2.4 DMF)
Bz-L-Ile-CAM	75	104-105	+11 (c 2.2 DMF)
Boc-L-Trp-CAM	85	154-158	-26 (c 2 DMF)

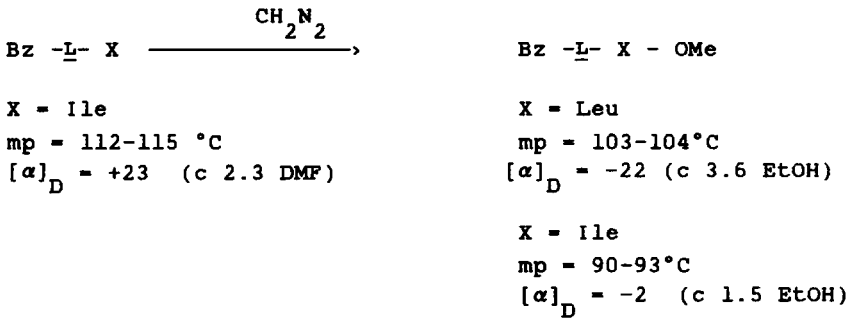
While removal of esters under normal conditions yields no satisfying results in peptide synthesis, the CAM esters can be cleanly and rapidly cleaved (10mn to 2 hr) by alkaline hydrolysis with a slight excess of NaOH 0.5N or Na_2CO_3 in DMF/water solutions. Sodium hydrogenocarbonate is also effective in removing CAM esters but the reaction time must be increased.

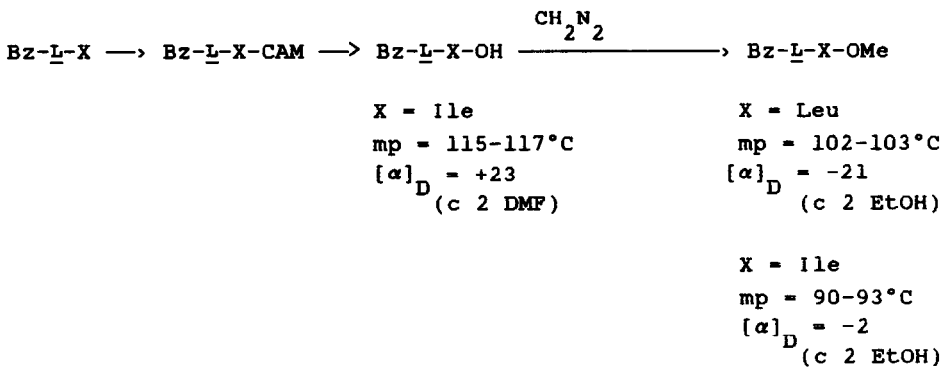
No racemization seems to occur during formation and cleavage of CAM esters of N-protected amino acids. To check this point, we prepared Bz-L-Leu-CAM and Bz-L-Ile-CAM. After hydrolysis of the CAM ester, both peptides were converted into their methyl esters by diazomethane (Scheme I). Methyl esters of these compounds[9] were compared with methyl esters of Bz-L-Leu and Bz-L-Ile obtained by direct esterification of the acids by diazomethane. All compounds showed a correct $[\alpha]_D$ and a correct melting point (see scheme I).

CAM esters may offer some advantages in peptide synthesis, particularly because they are stable under conditions of deprotection of other common protecting groups BOC, Z, FMOC, t-Butyl esters and because they are readily and cleanly removed under mild conditions which do not affect protecting groups such as BOC, Z or t-Butyl esters.

A more definitive evaluation of the CAM group for the protection of carboxyl functions requires further experimentation. Its application for the blocking of side chain carboxyl groups as well as its use in the synthesis of biological active peptides will also be investigated.

Scheme I.





More definitive tests of the CAM group and on its urethane equivalent will be subsequently reported.

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