Peptides

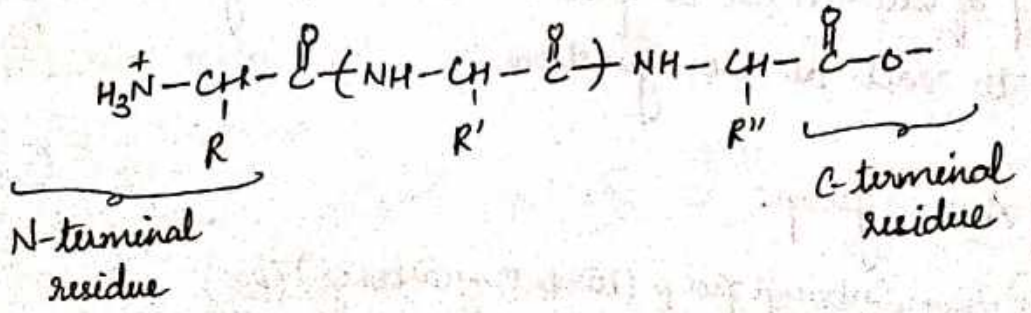
Peptides are amides formed by Condensation of amino group of one α amino acid with Carboxyl group of another molecule of same or different α- amino acid with elimination of water molecule.

Depending upon the number of amino acid residues per molecule they are known as dipeptide, Tripeptide and so on polypeptides

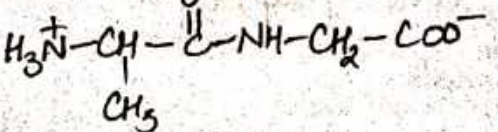
A number of amino acid units are joined with each other through $-\overset{O}{\overset{\|}{C}}-NH-$ linkage also known as peptide linkage.

In peptide formation, there is a free amino group at one end of the molecule known as N-terminal end and a free Carboxylic acid group at another end known as C-terminal end.

While writing the structure of polypeptide, the N-terminal is written at the left end and C-terminal at the right.



Peptides are named starting with the N-terminal amino acid residue

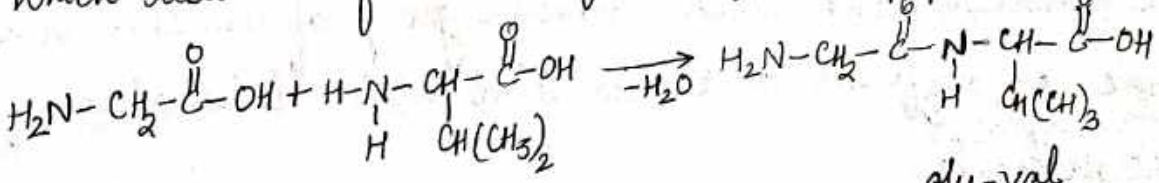


Alanylglycine (Ala-Gly)

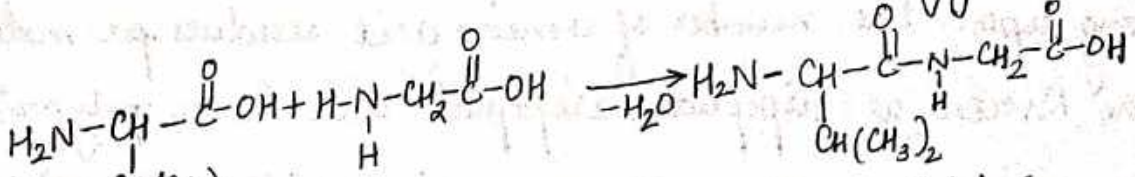
The names of amino acid residues involved in peptide linkages (all except the last) are given -yl suffix of acyl groups.

The alanine residue has the -yl suffix because it has acylated the nitrogen of glycine.

Synthesis of peptides (Example of combination of glycine and valine) which result in formation of ... different peptides.



gly-val



Valylglycine
(Val-gly)

Val-val and gly-gly are also formed.

In the synthesis of peptides, care must be taken to prevent the interaction of amino group of an amino acid with the carboxylic group of the same amino acid.

To exclusively synthesize glyc. valine, the $-NH_2$ group of glycine and $-COOH$ group of valine must be protected so that they are not freely available to react at these junctions.

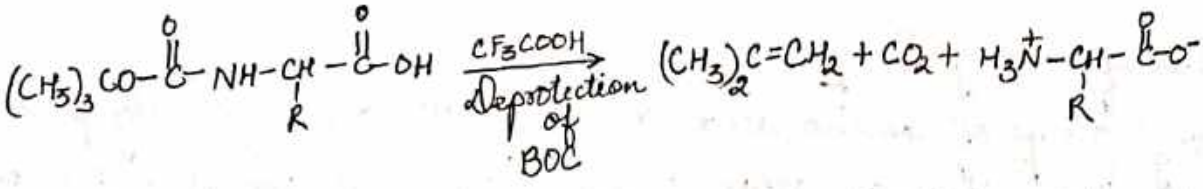
Protection of Amino group:

1. 1,1 Dimethylethoxycarbonyl group (tert-butoxycarbonyl) (BOC):

This group is abbreviated as BOC and is introduced into amino acid (for blocking amino group) by the reaction of amino acid with di-tert-butylcarbonate.

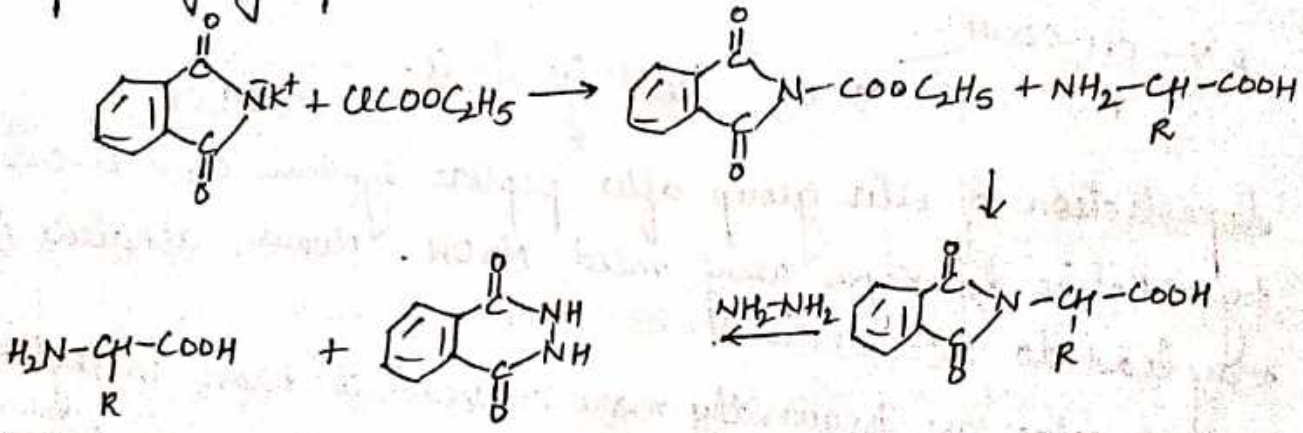
BOC-amino acid

The deprotection of tert-butoxycarbonylgroup (BOC) is carried out by treating the protected amino acid with HBr in presence of acetic acid or treating it CF_3COOH



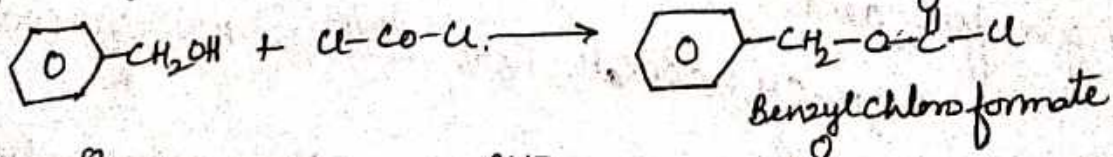
Phthaloyl Group

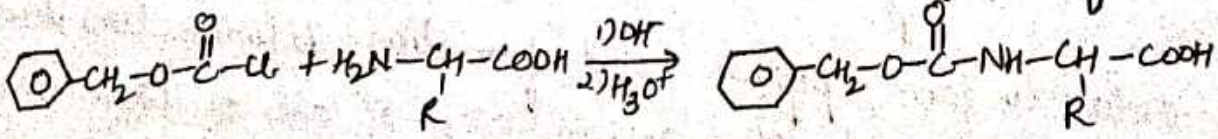
N-phthaloyl amino acids are obtained by condensing N-ethoxy Carbonyl phthalemide with amino acid in alkaline medium. The group can be can be cleaved by treating with hydrazine under refluxing conditions as N-phthaloyl group is sensitive to alkaline Conditions.

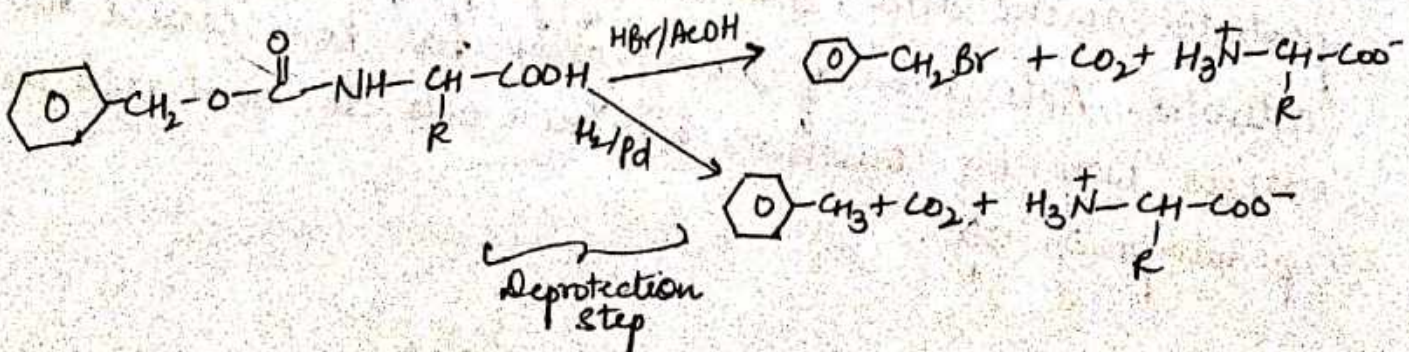


Benzyloxy carbonyl Group

In this method, we do acylation of the amino group by benzylchloroformate (Cbz)

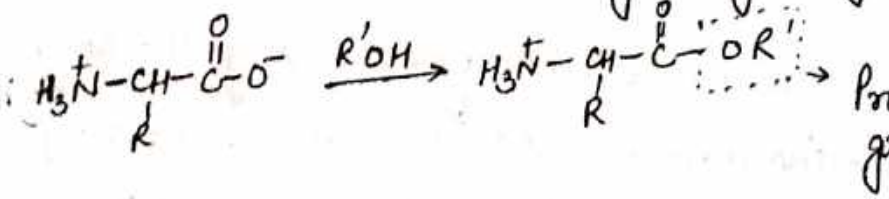


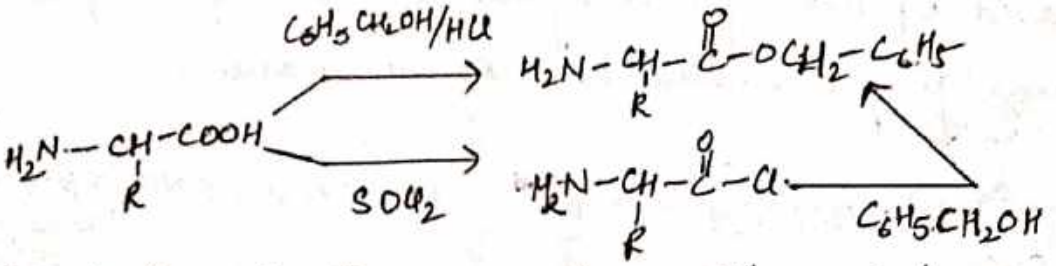




Protection of Carbonyl Groups:-

Carboxyl groups of amino acid and peptides are normally protected as esters, the common esters being methyl, ethyl, benzyl and t-butyl.

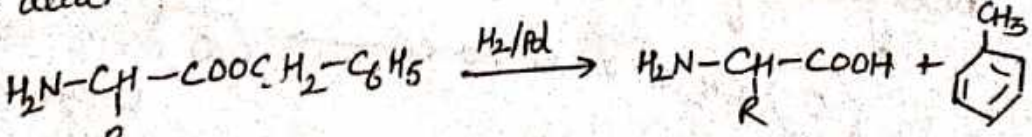




Deprotection of ester group after peptide synthesis can be carried out by alkaline hydrolysis using mild NaOH. However, alkaline conditions may lead to racemisation.

Benzyl esters are frequently more convenient than methyl or ethyl esters since they can be cleaved to the free acid by hydrogenolysis using H_2/Pd

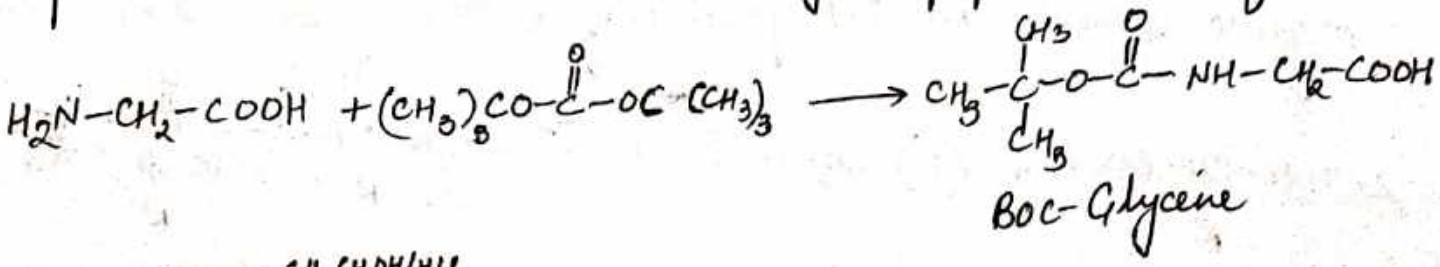
Treatment with HBr in acetic acid also removes the benzyl group to give free acid.



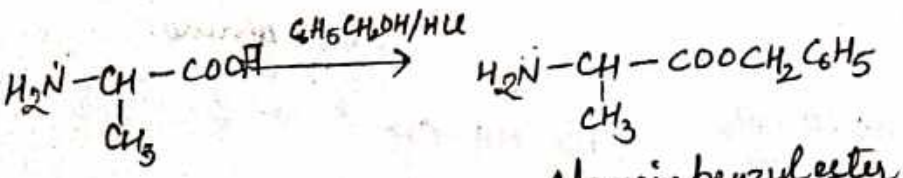
* So in order to form peptide bond formation between two suitably protected amino acid. Free carboxyl group of one of them must be activated. Activation of carboxyl group has been carried out in various ways, by conversion into acid chloride, acid azide, or p-nitrophenyl ester.

DCC Method

It is most important and widely used method, as it involves reaction b/w dicyclohexylcarbodiimide and suitably N-protected amino acid and C-protected amino acid, leads directly to peptide bond formation.



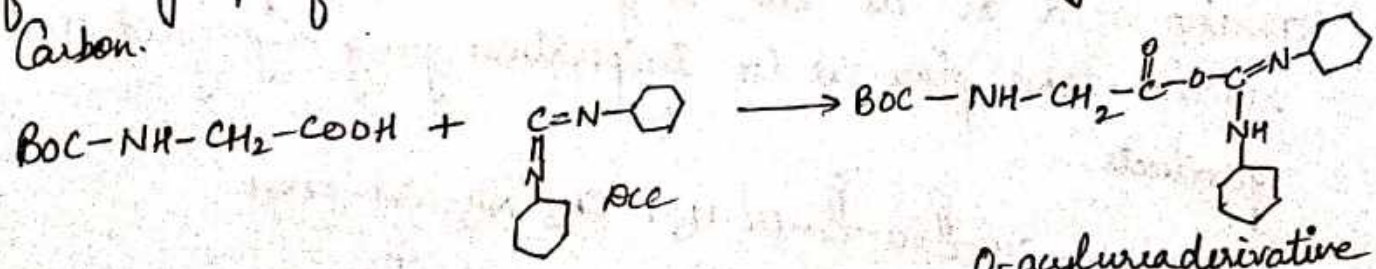
Boc-Glycine



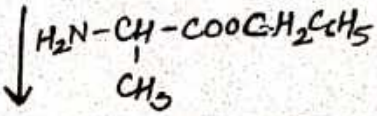
Alanine benzyl ester

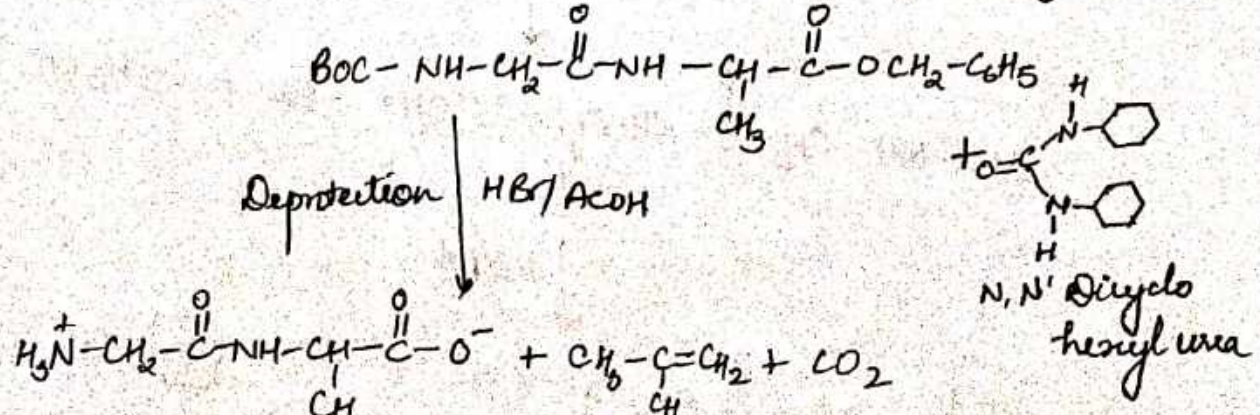
DCC- Coupling agent,

DCC activates the Carbonylic carbon so that the nucleophilic attack of amino group of another amino acid occurs readily at Carbonylic Carbon.



O-acylurea derivative



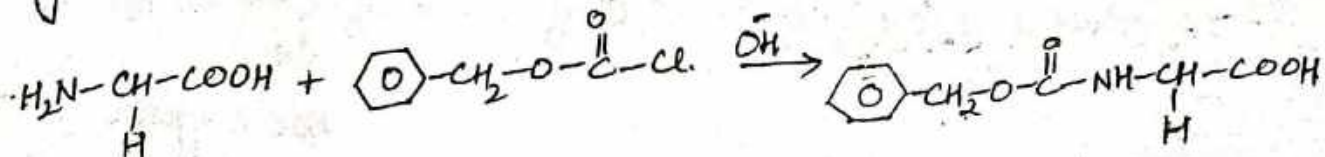


N, N' Dicyclo hexyl urea

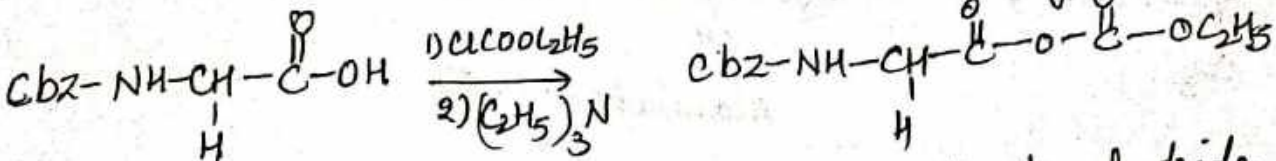
(glyAla)

Mixed Anhydride Method

In this method, the Carbonyl group of the protected amino acid is converted to mixed anhydride using ethyl Chloroformate in an organic Solvent in the presence of a tertiary base like triethylamine

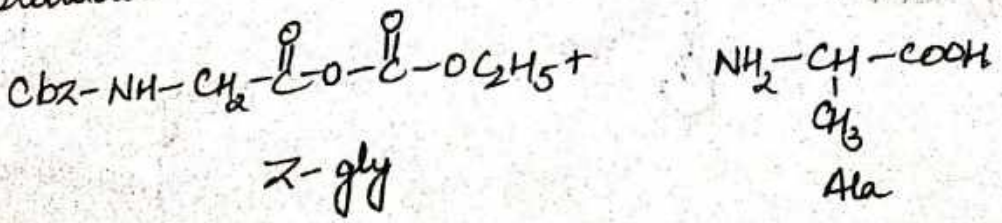


cbz-glycine



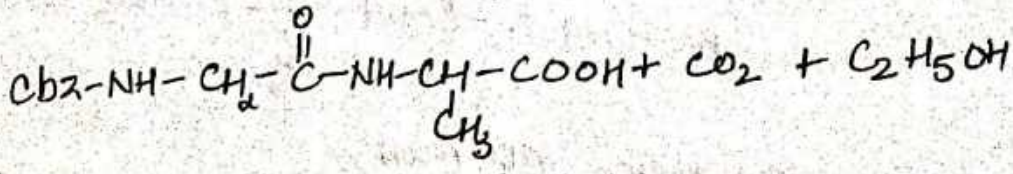
Mixed anhydride

The mixed anhydride can then be used to aylate another amino acid or its ester to give the desired product. The reaction takes place at low temperature giving high yield and pure products.



Z-gly

Ala



Gly-Ala