Protecting Groups for Amino Groups

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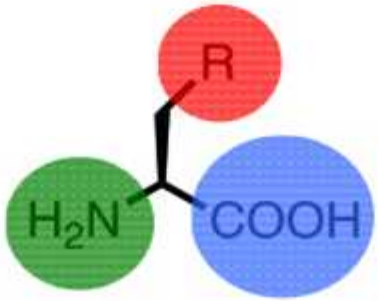
Protecting Groups (PG)

General Considerations

- Avoid undesired side reaction
- PGs have to be
  - Easily introduced and safely removed
  - Stable in reaction conditions
  - Orthogonal
- Which groups need protection?



If R contains NH_2, OH, SH, COOH or other reactive functionalities

The Concept of Protecting Functional Groups (PG)

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound, other reactive sites must be temporarily blocked.

A protecting group must fulfill a number of requirements:

- The protecting group should not have additional functionality that might provide additional sites of reaction.

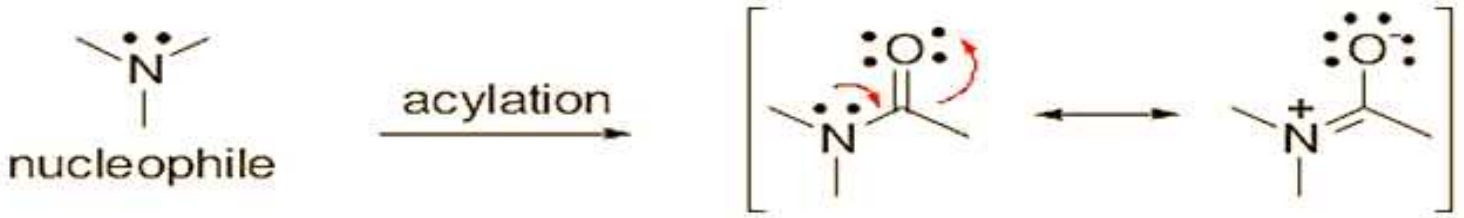
- The protecting group must be selectively removed in good yield by readily available reagents.

- The protecting group reagent must react selectively (kinetic chemoselectivity) in good yield to give a protected substrate that is stable to the projected reactions.

Why must an amino group be protected?

because it can contain **acid protons**	⟷	it can be **deprotonated** by strong bases
because it is a **nucleophilic site**	⟷	it reacts with **electrophiles**

The most general way of masking nucleophilicity is by **acylation**.



- Primary and secondary amines are prone to oxidation, and N-H bonds undergo metallationon exposure to organolithiumand Grignard reagents.
- Moreover, the amino group possesses a lone pair electrons, which can be protonated or reacted with electrophiles.
- To render the lone pair electrons less reactive, the amine can be converted into an amide via acylation.

Protecting Groups for Amino Groups

- Amine protection is often an essential part of synthetic organic chemistry as well as peptide synthesis. The abundance of amines in organic molecules makes the use of amine protecting groups commonplace in many synthetic schemes.

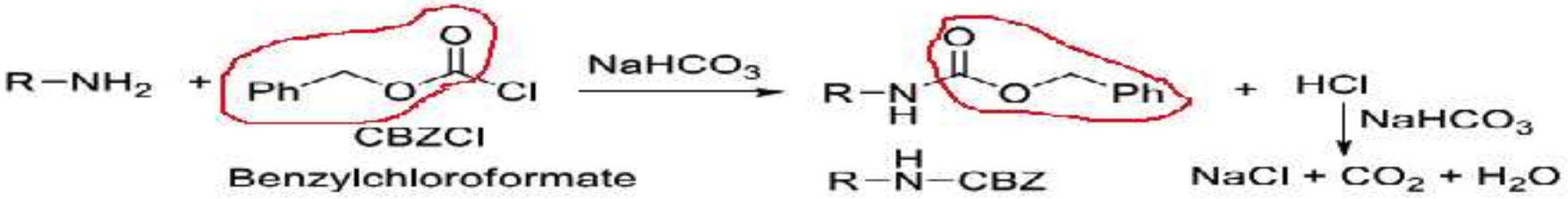
- Amines are nucleophilic and basic in nature and therefore can require protection to mask these properties during a chemical reaction. Effective protecting groups are able to be added to and easily removed from the compound being synthesized.

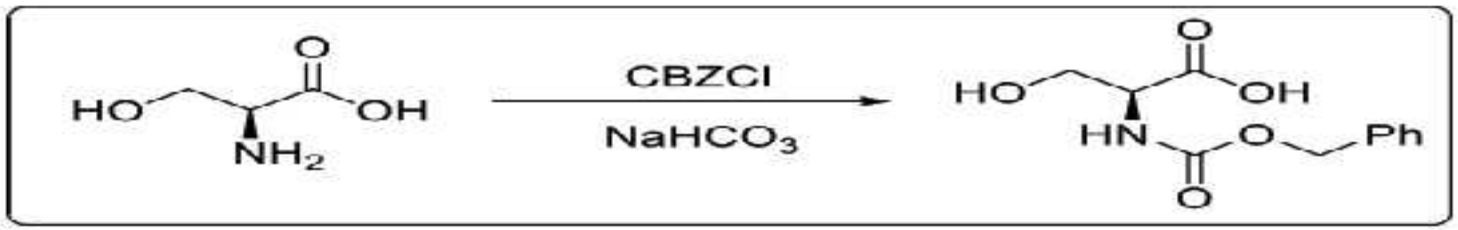
- In the case of amine protection, after the amine sensitive reaction is complete and the protecting group removed, the amine is regenerated as it was prior to adding the protecting group.

A - Protection of amino groups as carbamates

1- Benzyloxycarbonyl Protecting Group (CBZ):

PROTECTION:





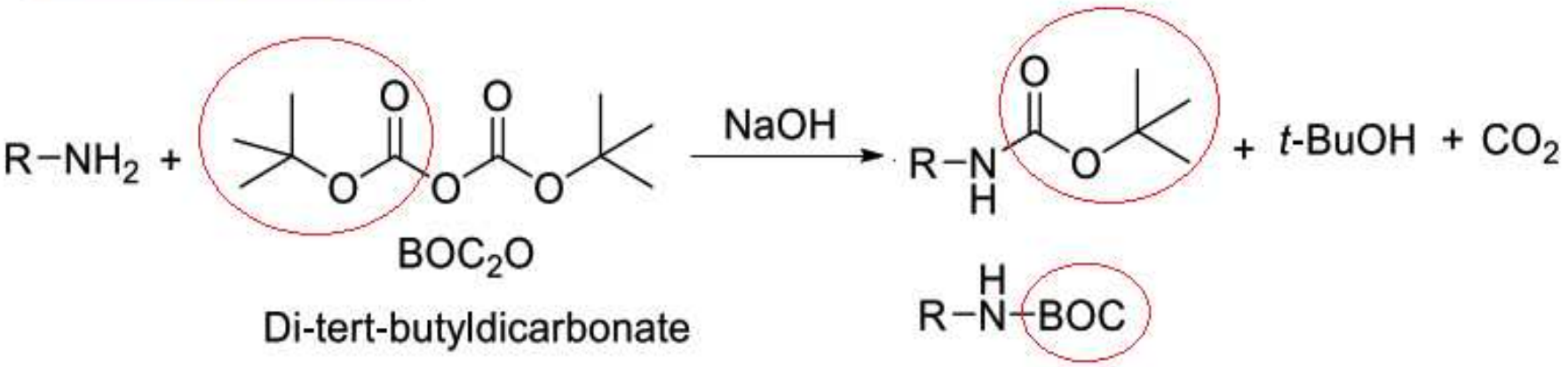
DEPROTECTION:

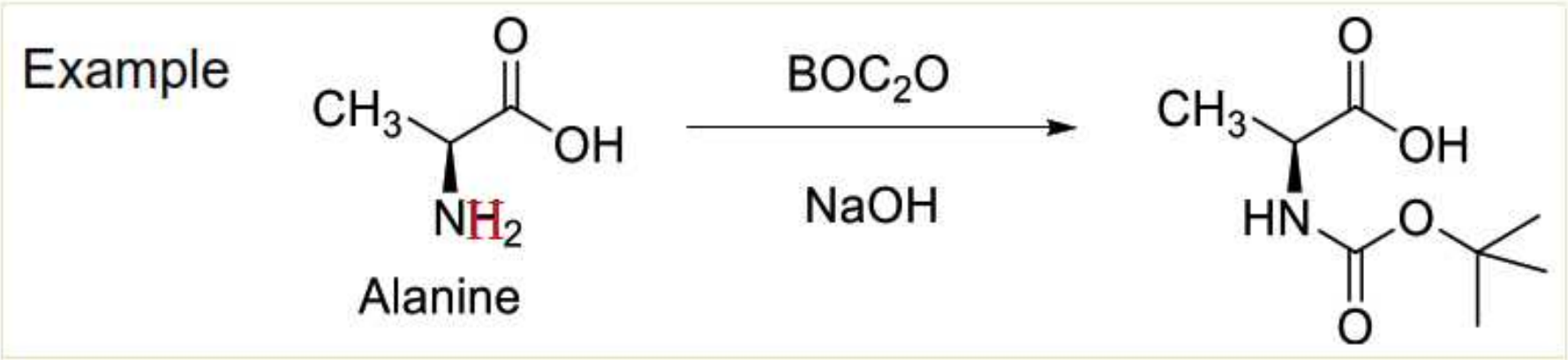
Because of the lability of the benzyl bond toward hydrogenolysis, the amine can be regenerated from a Cbz derivative by hydrogenolysis, which is accompanied by spontaneous decarboxylation of the resulting carbamic acid.

2) tert-Butyloxycarbonyl (t-Boc)

t- Butoxycarbonyl group(Boc) is inert to hydrogenolysis and resistant to bases and nucleophilic reagent.

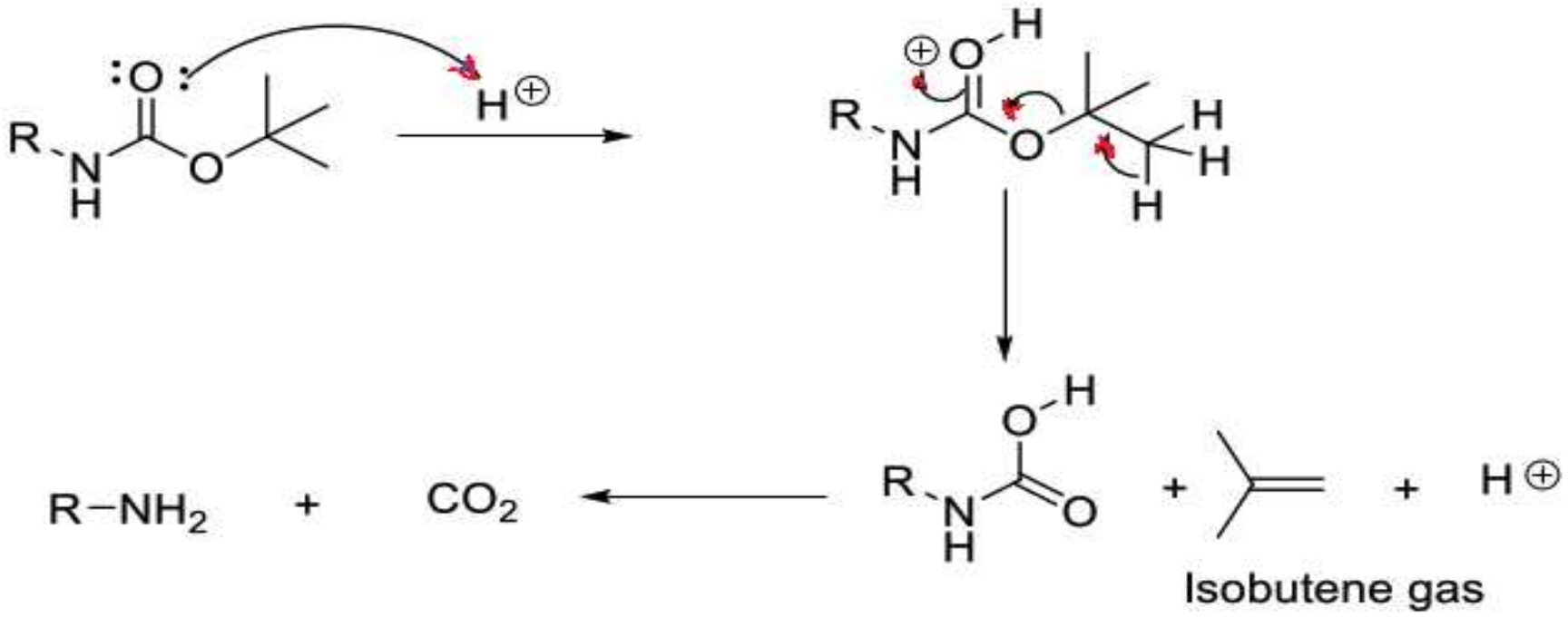
PROTECTION:

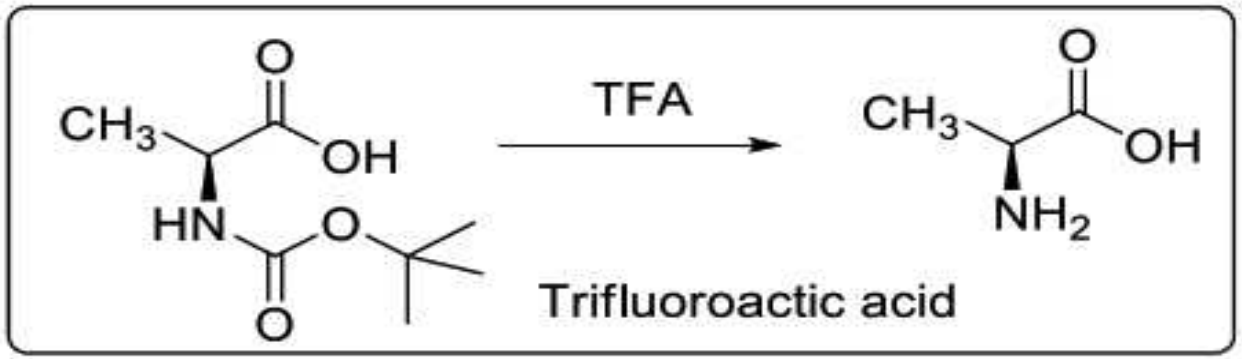




DEPROTECTION: (Cleavage)

Cleaved by strong acid CF3CO2H

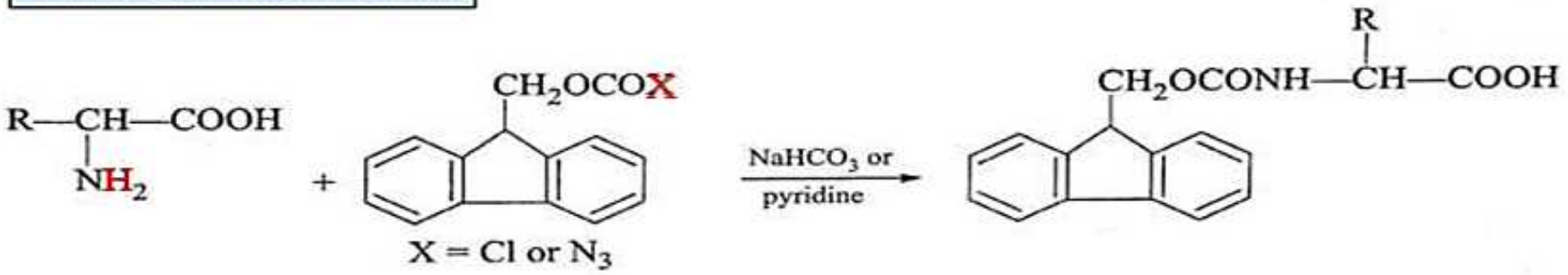




3- 9-Fluorenylmethyl carbamate (Fmoc or 9-fluorenylmethyloxycarbonyl):-

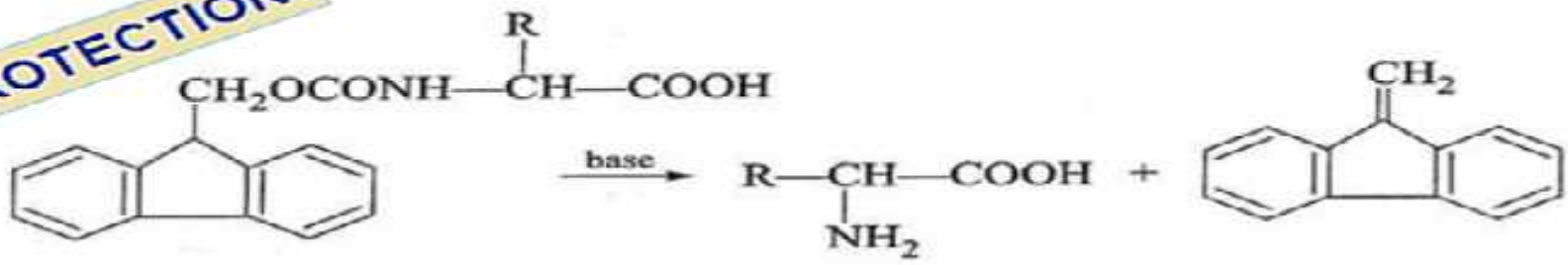
9-Fluorenylmethyloxycarbonyl protection is used for an alcohol or amine and it is carried out with an Fmoc—X reagent (X=Cl or N_3) in the presence of pyridine or $NaHCO_3$.

PROTECTION:

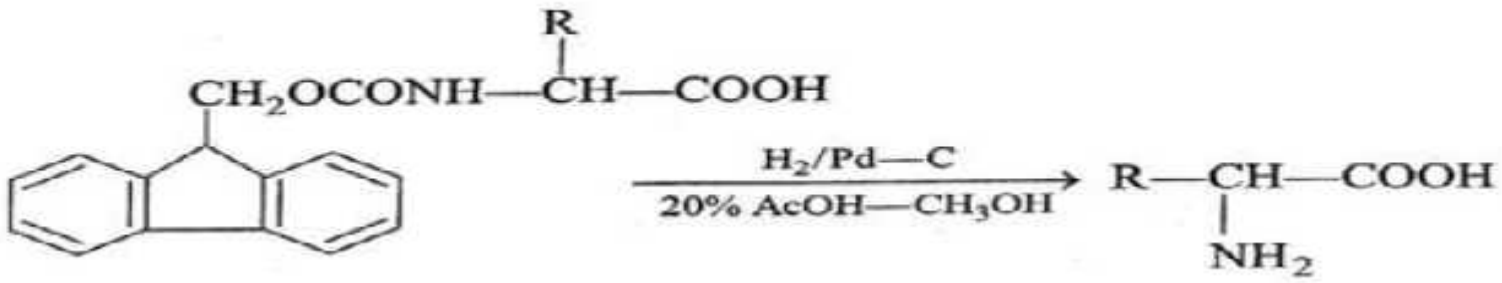


DEPROTECTION:

(i)



(ii)

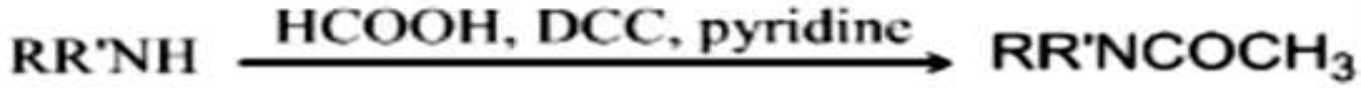


B-Protection of amino groups as amides

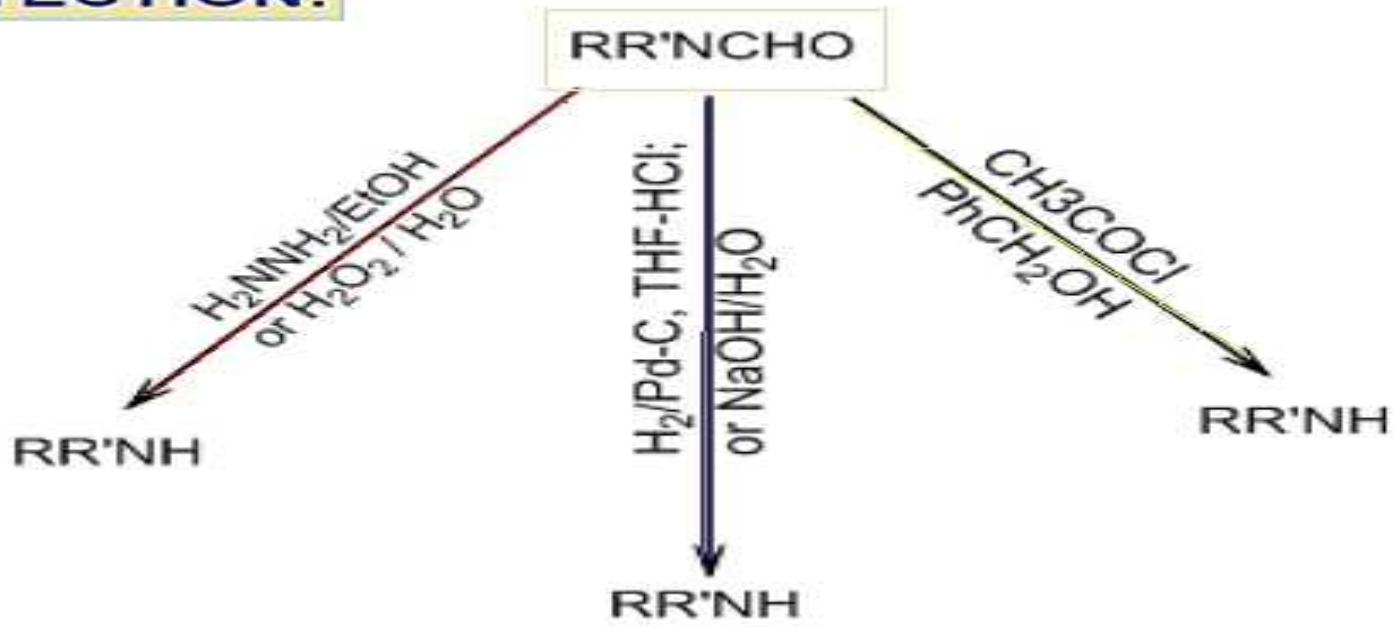
- **PROTECTION: formation of the amide starting from the corresponding** acyl chloride or anhydride
- **DEPROTECTION: the use of these amides is characterized by the** possibility of a **cleavage in mild conditions**

(a) Formamide (RR'NCHO):

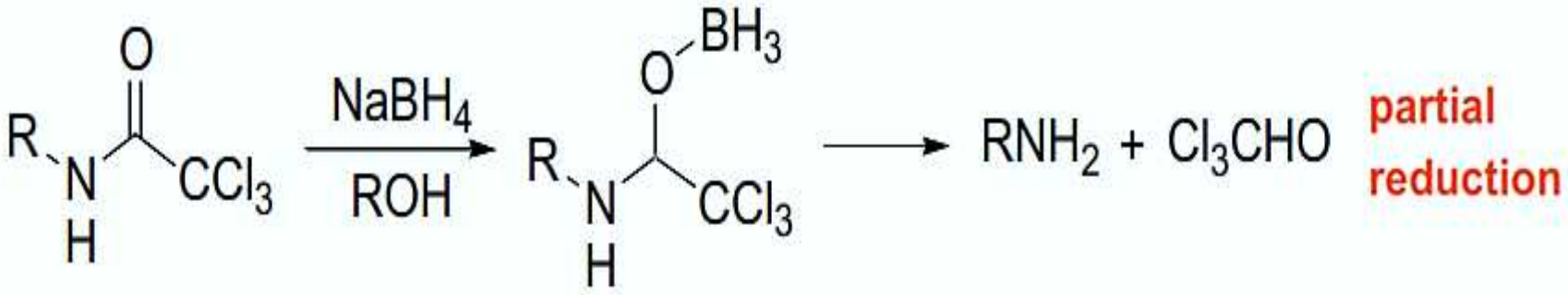
PROTECTION:



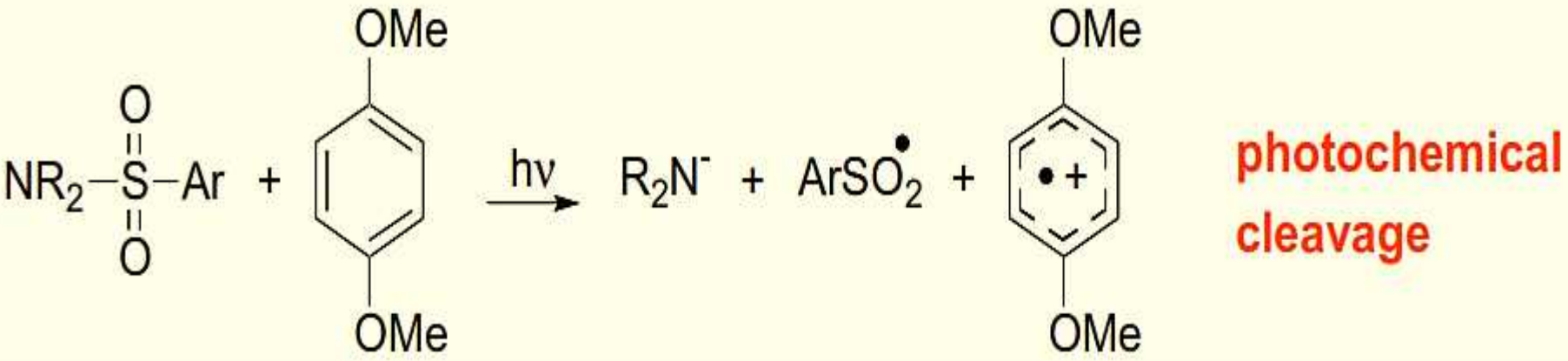
DEPROTECTION:



2) trichloroacetamides



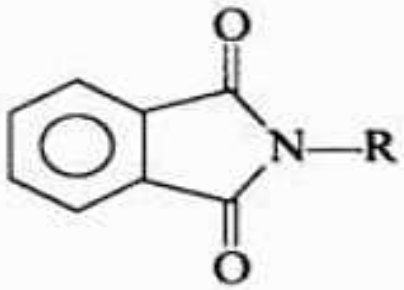
3) sulphonamides



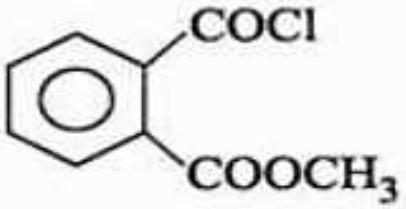
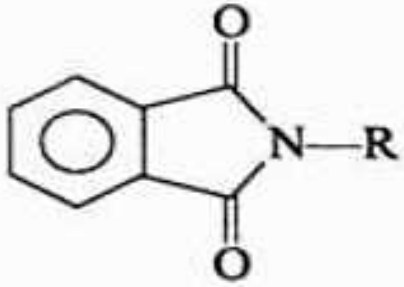
C- Cyclic Imides As Protecting Group For Primary Amines:-

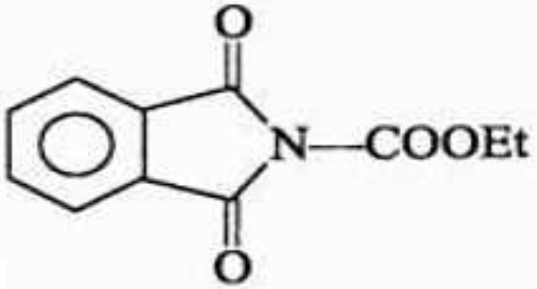
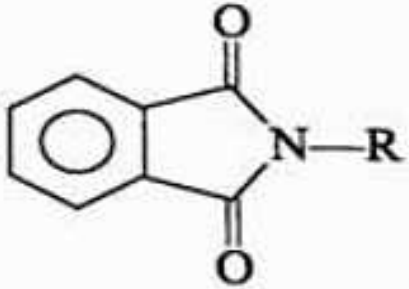
Phthalimide:-

PROTECTION:

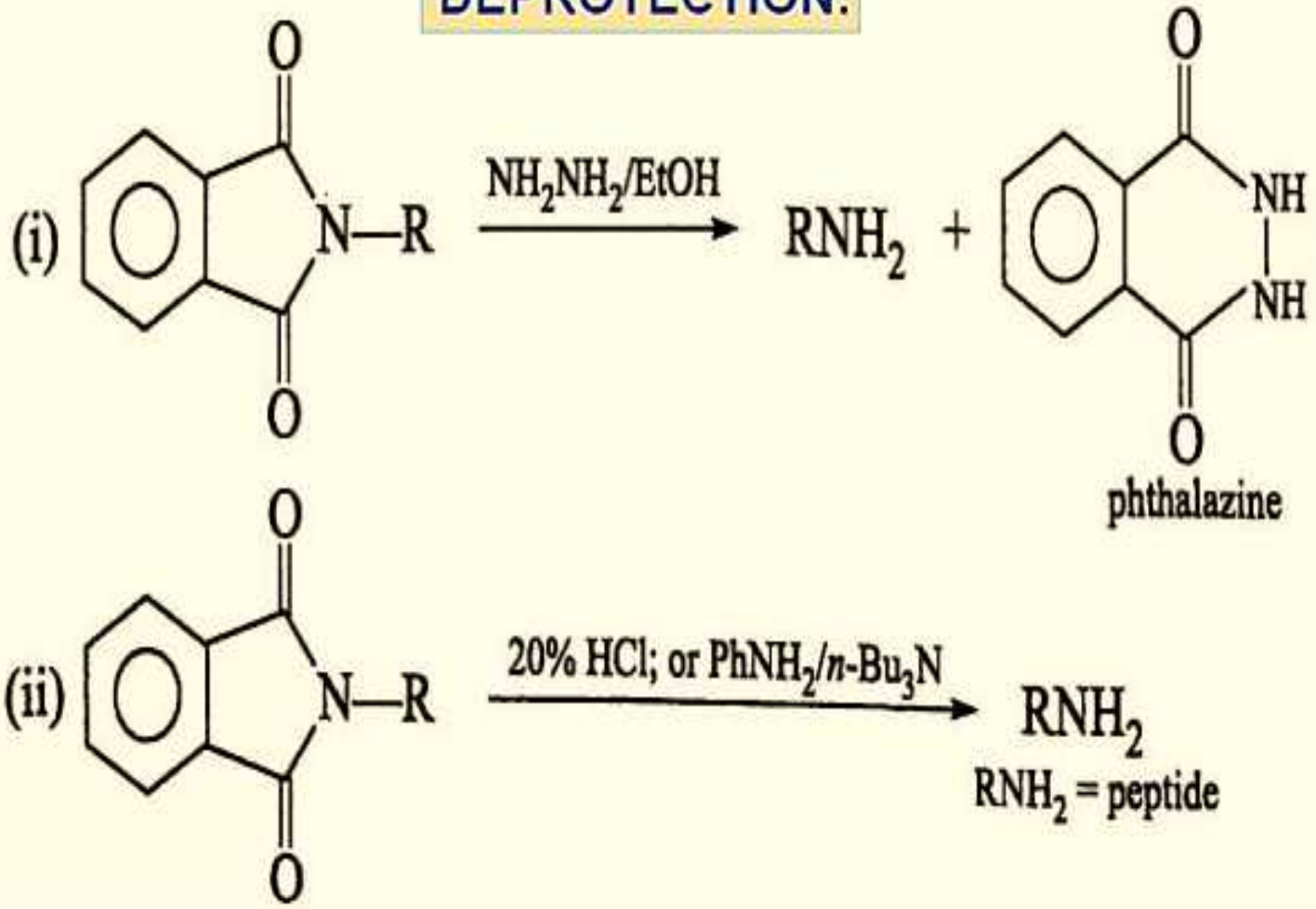
(i) RNH_2 + phthalic anhydride $\xrightarrow{CHCl_3}$ 

RNH_2 = nucleoside

(ii) RNH_2 +  $\xrightarrow{Et_3N/THF}$ 

(iii) RNH_2 +  $\xrightarrow{aq.\ Na_2CO_3}$ 

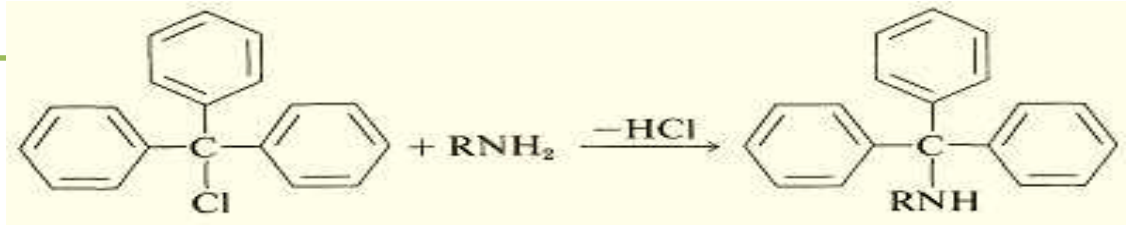
DEPROTECTION:



Other Methods:

Alkylation It is suitable for primary and secondary amines:

Triphenylmethyl is the most useful group of this type group $(C_6H_5)_3C-(C_6H_5)_3C-$, which can be introduced on the amine nitrogen by the reaction of triphenylmethyl chloride ("trityl" chloride) with the amine in the presence of a suitable base to remove the HCl that is formed:

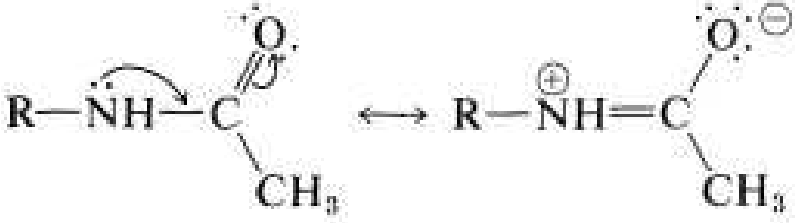


Acylation

One useful way of reducing the basicity and nucleophilicity of an amine nitrogen is to convert it to an amide by treatment with an acid chloride or acid anhydride

$$RNH2+CH3COCl \rightarrow RNHCOCH3+HCl$$

The reduced reactivity is associated with the stabilization produced by the attached carbonyl group because of its ability to accept electrons from the nitrogen atom "electron delocalization of the unshared pair of the amide function":

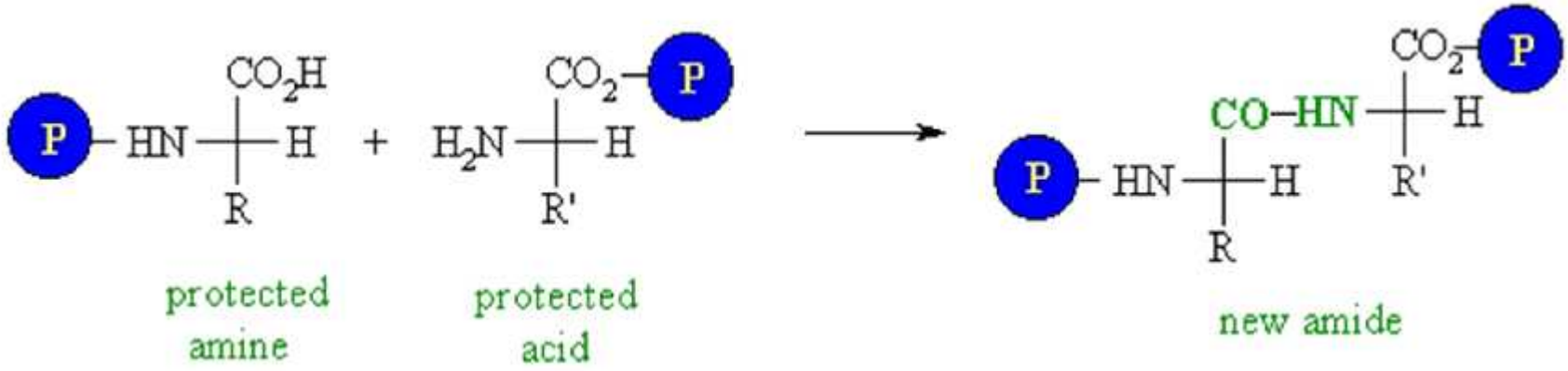


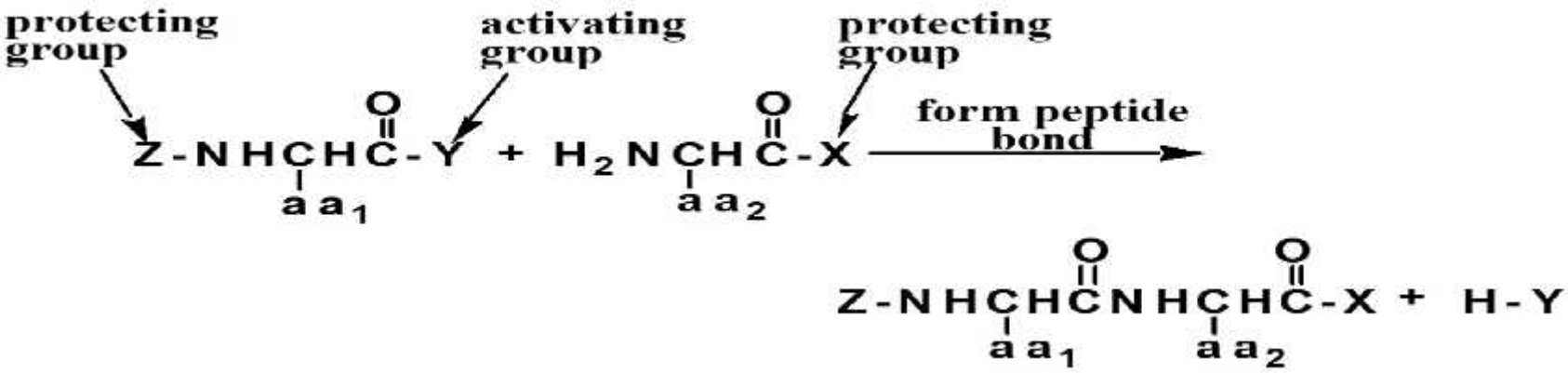
D- Peptide Synthesis : Protecting groups

Protein synthesis is important for several reasons including:

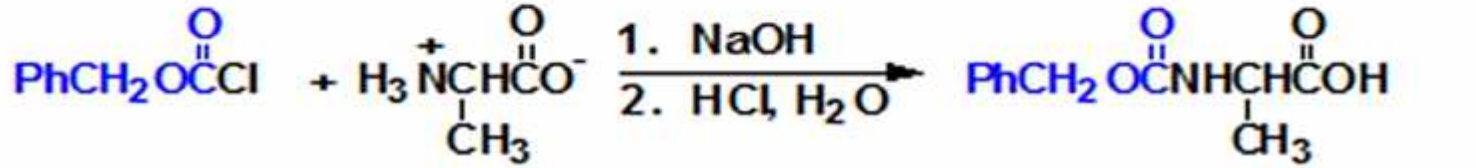
- confirming the structure of natural proteins (*e.g.* for medical research *etc.*)
- to investigate how protein structure and function are controlled by the amino acid sequence

However, it is not as straight forward as mixing the amino acids together to form the amides.
For example, a mixture of alanine, **A** and glycine, **G** would give a mixture of amides : **A-G**, **G-A**, **A-A** and **G-G**, plus higher polypeptides...)
In order to control the coupling reaction, it is necessary to use **protecting groups**.
By protecting the amine group of one component and the carboxylic acid group of the other, a specific amide bonds can be formed.



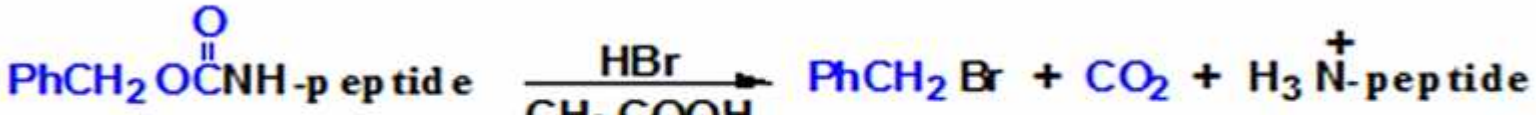


- Treatment of an amino group with <u>either</u> of these reagents gives a carbamate (an ester of the monoamide of carbonic acid).



Benzyloxycarbonyl chloride (Z-Cl) **Alanine** ***N*-Benzyloxycarbonylalanine (Z-Ala)**

- A carbamate is stable to dilute base but can be
- removed by treatment with HBr in acetic acid.



A Z-protected peptide **Benzyl bromide** **Unprotected peptide**

References

- Singh, J ; Yadav, L.D.S; Organic Synthesis;Pragati Publicaton; thirteenth edition- 2017; pp. 696-721.
- Kar, K.R.; Application of Redox and Reagents in Organic Synthesis; New Central Book Agency (P) Ltd; volume-1; pp 376-385.
- Clayden, J; Greeves, N; Warren, S; Wothers, POrganic Chemistry; pp 633-637 & 657.


THANK
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