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Chapter 1

Protection and Deprotection Chemistry

The presence of several functional groups in a molecule can greatly complicate the design of a synthesis, especially if a reagent reacts indiscriminately with the various functional groups present (for example, sugars). When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional com- pound, other reactive sites must be temporarily blocked. Thus, selection of protective groups plays an important part in planning a synthesis.

A protecting group must fulfil a number of requirements:

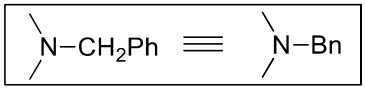
1. The protecting group reagent must react selectively (kinetic chemoselectivity) in good yield to give a protected substrate that is stable to the projected reactions.
2. The protecting group must be selectively removed in good yield by readily available reagents.
3. The protecting group should not have additional functionality that might provide additional sites of reaction.

Introduction of a protective group adds additional steps to a synthetic scheme. Hence, one should strive to keep the use of protecting groups to a minimum and avoid them if possible.

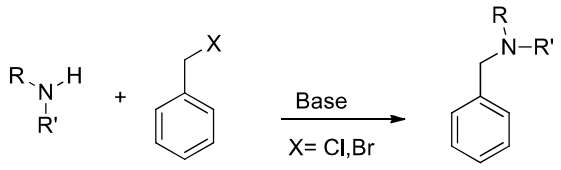
1.1 Protection of Amine Group:

- Primary and secondary amines are prone to oxidation, and N-H bonds undergo metalation on exposure to organolithium and Grignard reagents.
- Moreover, the amino group possesses a lone electron pair which can be protonated or reacted with electrophiles (R-X).
- To render the lone pair less reactive, the amine can be converted into an amide via acylation. Protection of the amino group in amino acids plays a crucial role in peptide synthesis.

1.1.1 N- Benzylamine:

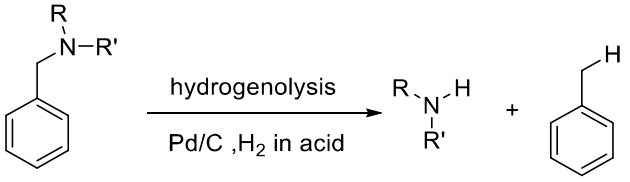


Formation: N-Benzyl groups (N-Bn) are especially useful for replacing the N-H protons in primary and secondary amines when exposed to organometallic reagents or metal hydrides.

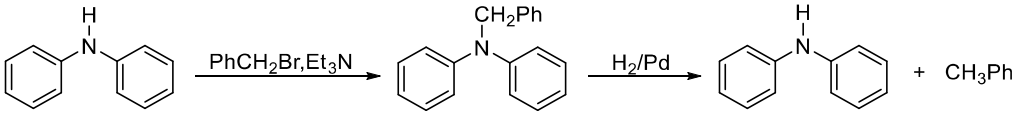


R' = H or alkyl or aryl

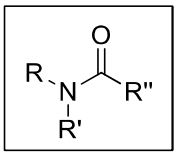
Cleavage: Hydrogenolysis of benzylamines with Pd catalysts and H, in the presence of an acid regenerates the amine



Example:

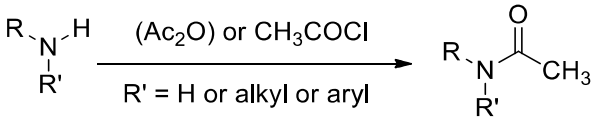


1.1.2 Amides

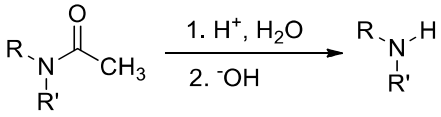


a. Acetamide:

Formation: Acylation of primary and secondary amines with acetic anhydride or acid chlorides furnishes the corresponding amides.

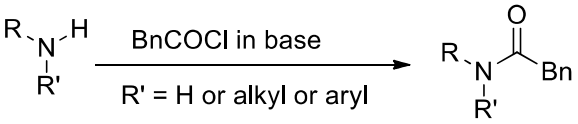


Cleavage: Acetamide is cleaved by strong acid (6N HCl, HBr) or diisobutylaluminumhydrid (DIBAL-H).

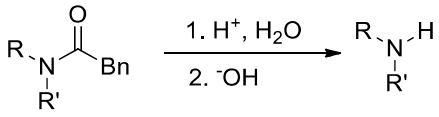


b. Benzamide:

Formation: Benzamides (N-Bz) are formed by the reaction of amines with benzoyl chloride in pyridine or trimethylamine.

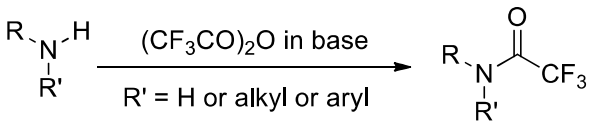


Cleavage: Benzamide is cleaved by strong acid (6N HCl, HBr) or diisobutylaluminumhydrid (DIBAL-H).

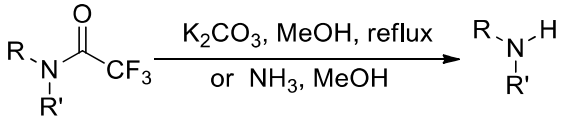


c. Trifluoroacetamides:

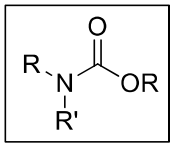
Formation: Trifluoroacetamides are formed by the reaction of amines with Trifluoroacetic anhydride in pyridine or trimethylamine.



Cleavage: Trifluoroacetamides is cleaved by base (K_2CO_3, MeOH, reflux) or NH_3, MeOH.

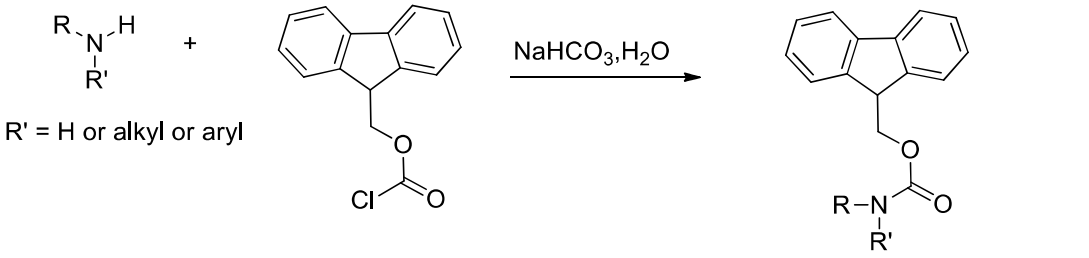


1.1.3 Carbamates

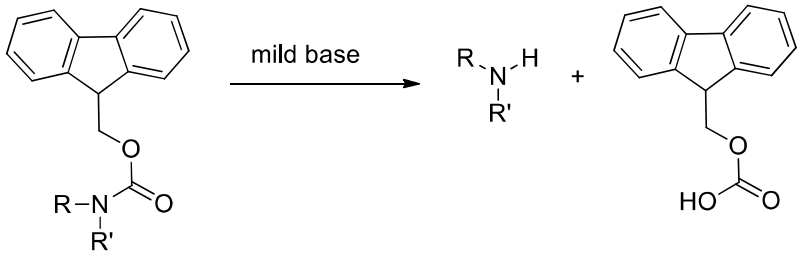


a. 9-Fluorenylmethyl Carbamate (Fmoc):

Formation:

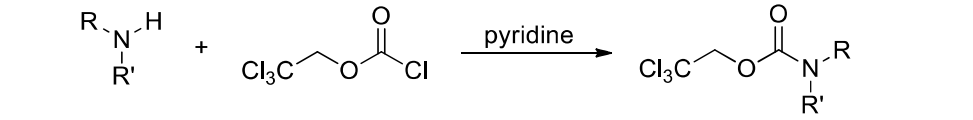


Cleavage: Cleaved with mild base such as piperidine, morpholine or dicyclohexylamine



b. 2,2,2-Trichloroethyl Carbamate:

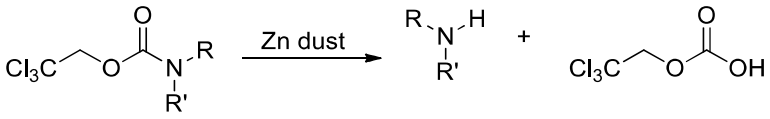
Formation:



R' = H or alkyl or aryl

2,2,2-Trichloroethyl Carbamate

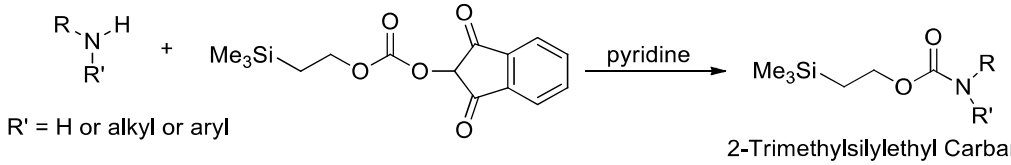
Cleavage: Cleaved with zinc dust or electrochemically.



Example:

c. 2-Trimethylsilylethyl Carbamate (Teoc):

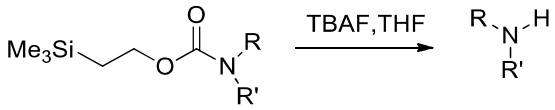
Formation:



R' = H or alkyl or aryl

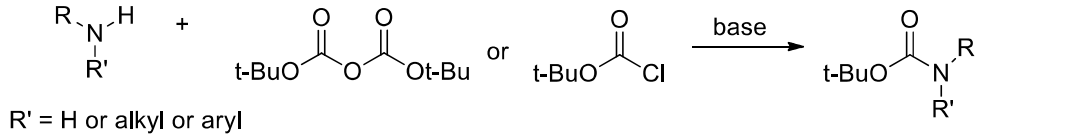
2-Trimethylsilylethyl Carbamate (Teoc)

Cleavage: Cleaved with fluoride ion source such as TBAF, CsF, HF, etc....



d. t-Butyl Carbamate (BOC):

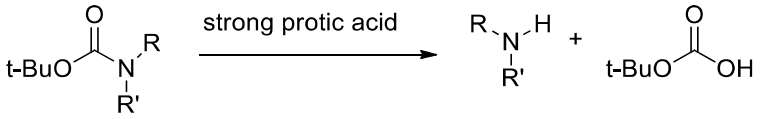
Formation:



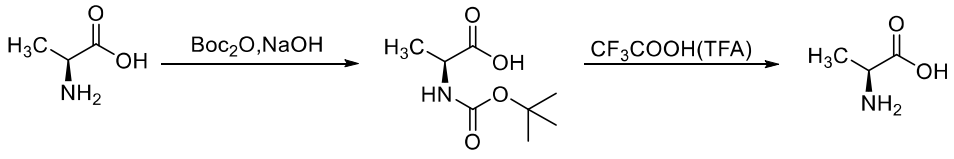
R' = H or alkyl or aryl

t-Butyl Carbamate (BOC)

Cleavage: Cleaved with strong protic acid (3M HCl, CF_3COOH), TMS-I.

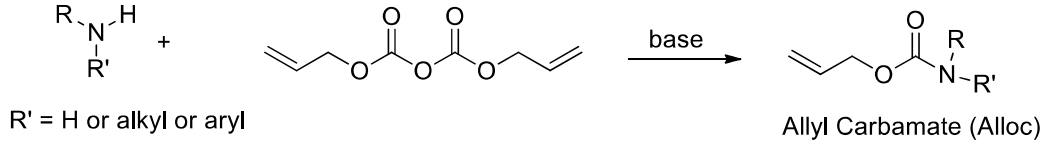


Example:

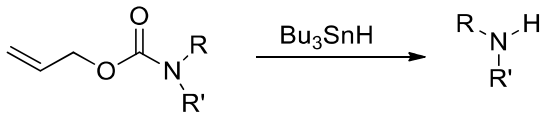


e. AllylCarbamate (Alloc):

Formation:

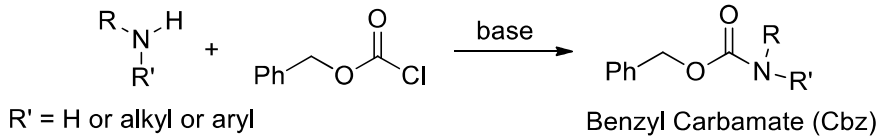


Cleavage: removed with Pd(0) and a reducing agent (Bu_3SnH, Et_3SiH, HCO_2H).

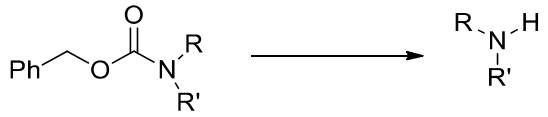


f. Benzyl Carbamate (Cbz):

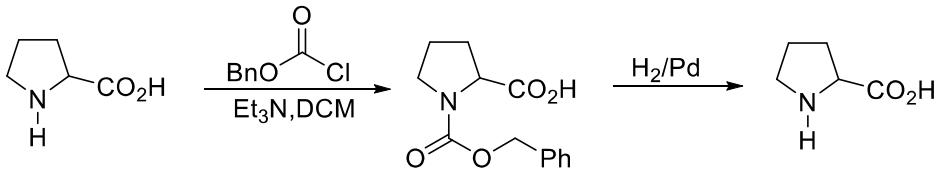
Formation:

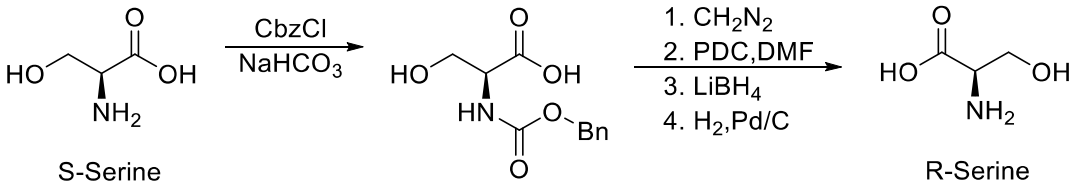


Cleavage: Removed with Hydrogenolysis ($Pd/C,H_2$), $PdCl_2$, Et_3SiH,TMS-I, BBr_3, hv (254 nm),Na/ NH_3.



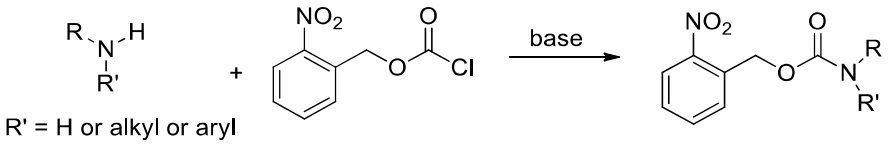
Example:





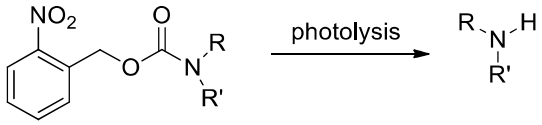
g. m-NitrophenylCarbamate:

Formation:

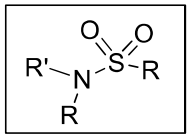


R' = H or alkyl or aryl

Cleavage: cleaved by photolysis.

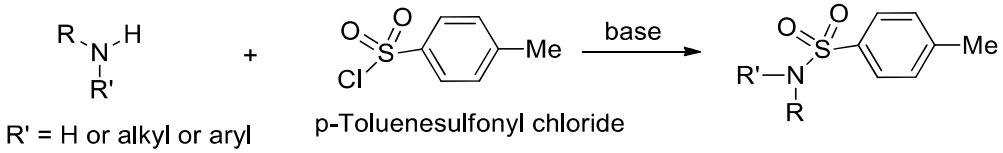


1.1.4 Sulfonamides



a. p-Toluenesulfonyl (Ts):

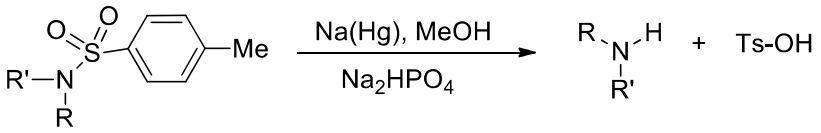
Formation:



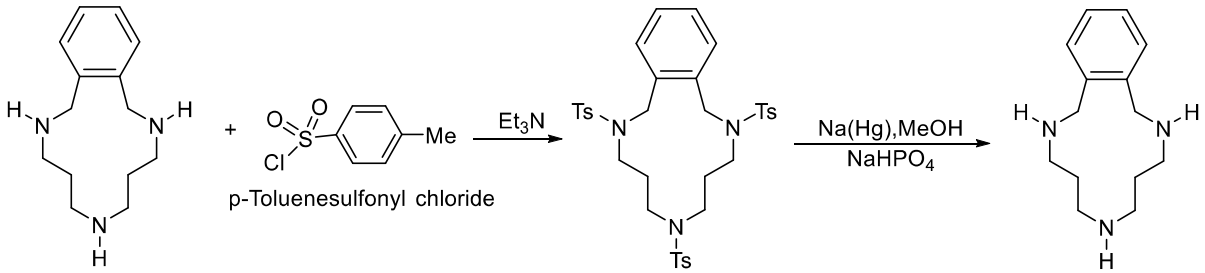
R' = H or alkyl or aryl

p-Toluenesulfonyl chloride

Cleavage: Strong acid, sodium Naphthalide, Na (Hg)

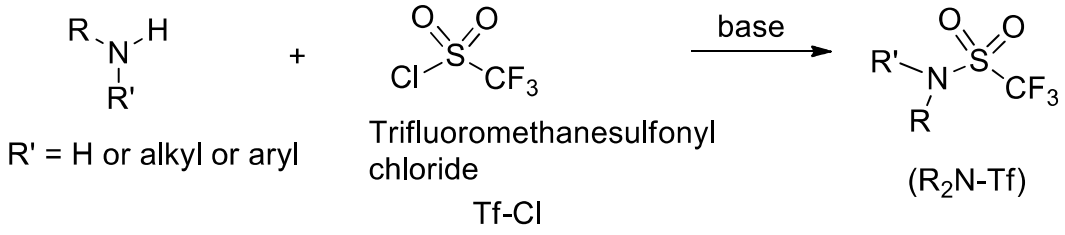


Example:

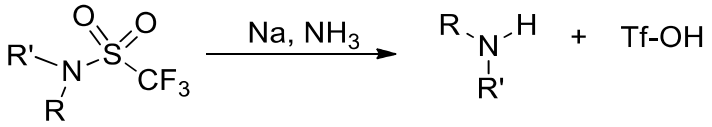


b. Trifluoromethanesulfonyl:

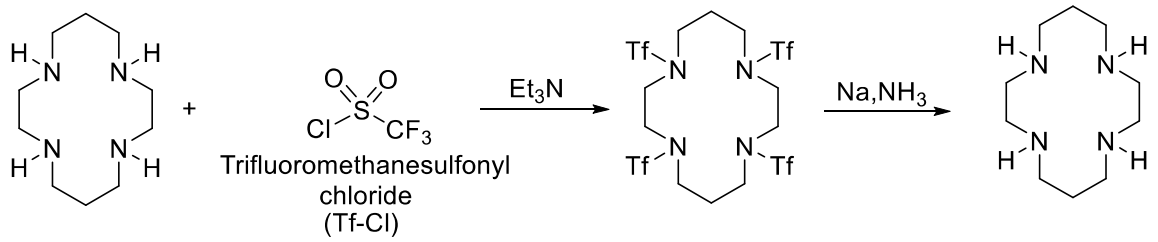
Formation:



Cleavage: cleaved by Na, NH_3.

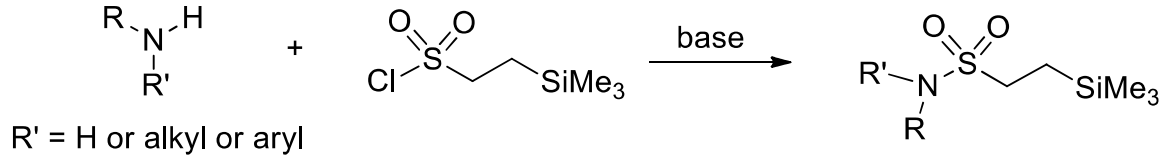


Example:

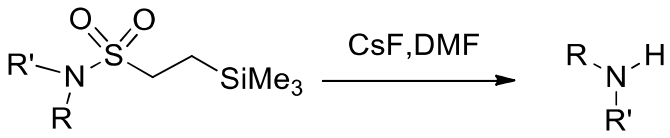


c. Trimethylsilylethanesulfonamide (SES):

Formation:



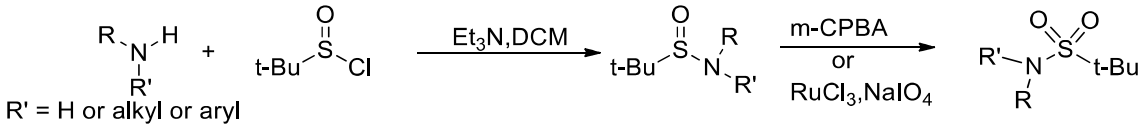
Cleavage: cleaved with fluoride ion.



Example:

d. tert-Butylsulfonyl (Bus):

Formation:



Cleavage: cleaved by CF_3SO_3H, CH_2Cl_2 in anisole.



Example:

1.2 Protection of OH Group of Alcohol

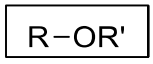
The most important protecting groups for alcohols are ethers and mixed acetals. The proper choice of the protecting group is crucial if chemoselectivity is desired.

Reactivity of alcohols: I° alcohol > 2° alcohol > 3° alcohol.

All ethers are stable to basic reaction conditions. Hence, ether or mixed acetal protecting groups specifically tolerate:

I. RMgX and RLi reagents.
II. Nucleophilic reducing reagents such as $LiAlH_4$ and $NaBH_4$.
III. Oxidizing agents such as CrO_3.2 pyridine, pyridiniumchlorochromate (PCC), and MnO_2.
IV. Wittig reagents.
V. Strong bases such as LDA.

1.2.1 Alkyl Ethers:



a. Methyl ether:

Formation:

method1:



method 2:

