3.8.Concept in Organic Synthesis

3.8.1. Disconnection Approach or Retrosynthesis

A logical approach for designing organic synthesis involving breaking down of the target molecule into the corresponding starting materials by imaginary breaking of bonds and by functional group interconversion (FGI) is called disconnection approach or retrosynthesis.

A double line arrow is called a retrosynthetic arrow. e. g. a molecule Z can be synthesized from X and Y, so the retrosynthetic pathway is as shown below

$$z \longrightarrow x + y$$

disconnection

$$O_2N$$
 O_2N
 O_2N
 O_2N
 O_2N
 O_2N
 O_2N

3.8.2. Synthons

Synthons are basically idealized fragments or reagents (usually cations and anions) resulting from a disconnection approach.

3.8.3. Convergent and Linear Synthesis

- A reaction with aiming to improve the efficiency of multi step chemical synthesis is known as Convergent synthesis. It is applied for the synthesis of complex molecules involving fragment coupling.
- In linear synthesis the overall yield quickly drops with each step of the reaction.

3.8.4.Umpolung

- The term Umpolung is a German word, which means reversal of polarity.
- Umpolung refers to reversal of normal polarity of a functional group (electrophilic group changes to nucleophilic and vice versa).

electrophilc in nature due to electronegativity difference of carbon and oxygen nucleophilc in nature due to negative charge on carbon

3.8.5. Protecting Groups

- In presence of two different functional groups in a molecule, the more reactive functional group may react alone, but it may not be possible to react the less reactive group selectively.
- The presence of which makes the less reactive group to react selectively and ultimately affords the desired product is called protecting group.

Acetoacetic ester

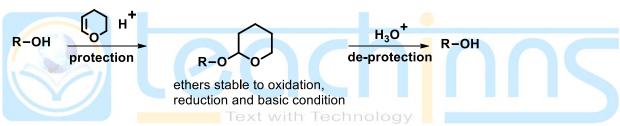
tertiary alcohol

- Let us consider the synthesis of a tertiary alcohol from acetoacetic ester.
- In this molecule two different functional groups (keto- and ester-) are present among which keto group is more reactive than the ester group.
- Therefore, with the addition of Grignard reagent, it immediately reacts the keto group and hence the undesired product is formed (as shown in equation i).

- But if we protect the keto group with the help of ethylene glycol, then the Grignard reagent will react with the less reactive ester functionality and ultimately affords the desired product under acidic hydrolysis (as shown in equation ii).
- ❖ **Properties of protecting groups**: Any protecting group must follow the following conditions like
- (a) Very easy to put on and the reaction will be high yielding.
- (b) Very easy to remove in high yield.
- (c) The protecting group must be stable under the reaction condition.

Protecting groups for alcohols

(a) Acetals or ketals as protecting groups for alcohols: Acetals or ketals are not only used as protecting groups for aldehyde and ketones, but they also can be used for the protection of alcohols.



(b) Ethers as protecting groups for alcohols:

$$R-OH \xrightarrow{\text{DMF, NaH}} Ph \xrightarrow{\text{Ph}} \frac{H_2, Pd/C}{\text{de-protection}} R-OH$$

ethers stable to oxidation, reduction and basic condition

- **Protecting groups for Carboxylic acids**
- (a) Esters as protecting groups for carboxylic acids:

R-COOH

$$\begin{array}{c}
CH_3OH, H^{+} \\
\hline
\text{protection}
\end{array}$$

R-COOCH₃

$$\begin{array}{c}
\text{(i) Me}_3SiCI \\
\hline
\text{(ii) Nal, CH}_3CN
\end{array}$$

R-COOH

$$\begin{array}{c}
\hline
\text{R-COOH} \\
\hline
\text{TsOH, DCM} \\
\text{protection}
\end{array}$$

R-COOH

$$\begin{array}{c}
AcOH, \\
\hline
\text{THF-water}
\end{array}$$

R-COOH

(b) Amides as protecting groups for carboxylic acids:

$$R-COOH \xrightarrow{R'R"NH} R-CONR'R" \xrightarrow{HNO_2} R-COOH$$

$$PPh_3 R-CONR'R" \xrightarrow{KOH, OH(CH_2)_2OH} R-COOH$$

- **❖** Protecting groups for Amines
- Carbamates as protecting groups for amines: