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RETROSYNTHESIS APPROACH FOR ORGANIC COMPOUNDS

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Abstract :

RETRO- Backward: SYNTHESIS – TO MAKE MOLECULES.

Retrosynthetic Analysis is a technique for solving problems in the planning of "Organic Syntheses" the logical process of analysis the structure of a target molecule to discern a possible synthesis step by step. In this approach, a strategic bond is **broken or disconnected** (by mental process) to give, generally two charged species called **Synthons**. Generally, Synthons- Not available commercially. Their synthetic equivalents are available or can be easily synthesized. The strategic bond (which is disconnected) is contained in **Retron**. The functional group containing portions of the target molecule is called Retrons. These imaginary backward reactions are known as **Antithetical Reactions.** Retrosynthetic analysis is based on known reactions such as **Witting Reaction, Oxidation, Reduction.** Retrosynthesis is a technique planning a synthesis, especially of complex organic molecules, whereby the **Target Molecule (TM)** is reduced into a sequence of progressively simpler structures which leads to the identification of a simple **Starting Material (SM)** from which a chemical synthesis can be developed.

Disconnection for Retrosynthesis: This is the process of synthesis design which starts with the product and works backward towards the starting material. The disconnection of strategic bond of target molecule is denoted by a **hollow arrow (Only denote Breakdown Molecule (TM) not for Chemical reactions).**

DISCONNECTIONS:C-X (X= N, S, O) – Hetro-Atom with Carbon.
C-C (C1 – C2) – 1,2-, 1,3-, 1,4- ,1,5-,1,6- Difunctional groups.

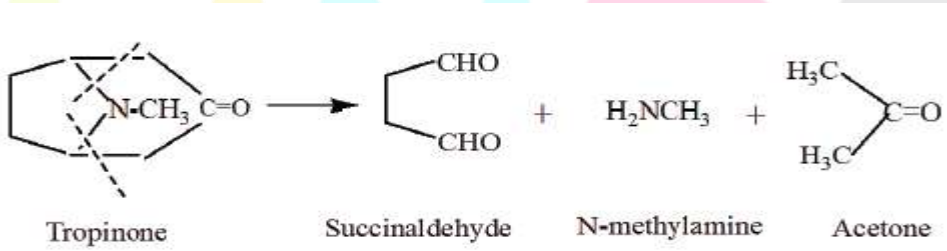
Key Words: FGI, FGA, FGR, FGT, TM, SM, (dn), (an), Synthons, Retrons, Disconnections, synthetic planning,

INTRODUCTION:

Organic compounds are diverse in nature and their applications. They have utilities in all walks of life including food, pharmaceuticals, cosmetics, polymers, detergents etc. One of the major tasks that the organic chemists face is their synthesis. **Disconnection approach** is a helping tool for the design of their synthesis. This is also known as the **Retrosynthetic analysis.** This is the reverse method of observing a molecule keeping their synthesis in mind. This is a synthetic route to the target molecule from the simpler molecule or simpler starting materials. This approach of "**Disconnection"** to synthesis is now a basic part of every organic synthesis route.

The advent of retrosynthetic analysis constituted a major advance in the strategic planning of total synthesis of natural and complex compounds. Retrosynthetic analysis is a problem-solving technique for the synthesis of complex molecules. It is the art of planning organic synthesis by transforming the structure of the desired molecule to simple commercially available starting materials for its synthesis. Transformation of a molecule to its synthetic precursor is done by the imaginary disconnection of its bonds to progressively simple structures along a pathway which ultimately leads to simple or commercially available Retrosynthetic analysis is the exact reverse (antithetic) of a synthetic reaction. However, the first notable example of a product being transformed into its synthetic precursors was that of Robinson's tropinone synthesis. starting materials for the synthesis. At each step, the availability of the intermediate is evaluated. Retrosynthetic analysis is the exact reverse (antithetic) of a synthetic reaction. However, the first notable example of a product being transformed into its synthetic precursors was that of Robinson's Tropinone synthesis.

Tropinone was submitted to imaginary hydrolysis at the points indicated by the dotted lines below and resolved into succinaldehyde, methylamine and acetone. The precursors were identified from the starting material, and then a suitable path was devised to convert these starting materials into the target molecule using known reactions.



"Retrosynthetic (or antithetic) analysis is a problem-solving technique to convert the structure of a synthetic target (TGT) molecule to a series of gradually simpler structures *via* a path which finally indicates to simple or commercially available starting materials for a chemical synthesis."

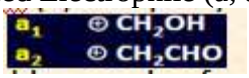
The main goal of a retrosynthetic analysis should be to reduce the molecule to similarly sized building blocks of lower or similar complexity. This process of simplification should be continued until you reach molecules which are commercially available.

Terms and Definitions:

- **Target Molecule (TM):** The molecule to be synthesized.

- **Retrosynthetic Analysis:** The process of imaginary breaks down of a molecule into progressively simpler starting materials. The reactions are viewed in the retrosynthetic direction i.e., starting with the product and going back to the reactants along a pathway that is reverse of a synthetic direction.

- **dn - synthon**: Functionalized Nucleophile (d, donor) with the hetero atom of the functional group joined to the nth C- atom. 

- **an- synthon**: Functionalized Electrophile (a, acceptor) with the hetero atom of the functional group joined to the nth C- atom. 

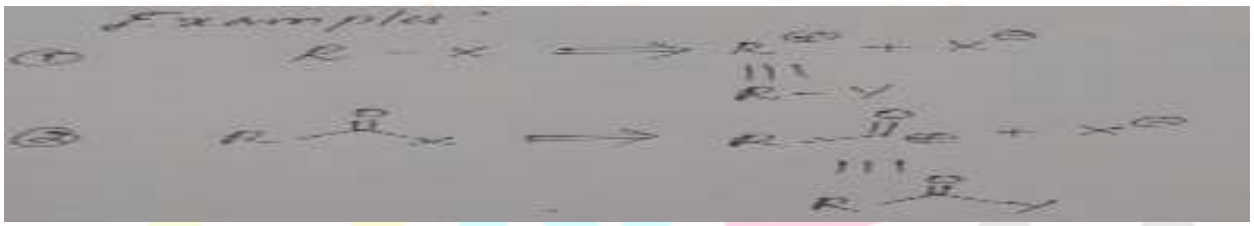
- **Tft :** Such disconnections are called as transforms.

- **Synthetic Equivalent**:(▬) It is repeated until simplest synthetic equivalents are obtained. The disconnected product of first transform act as the TM of the second disconnection and successively till the simple disconnected SM (Precursor) was obtained.

Other Synthons and their Synthetic equivalents

- **Retrosynthetic (or antithetic) analysis**:

Retrosynthetic (or antithetic) analysis is a problem resolving method for converting the structure of a synthetic target (TGT)molecule to a sequence of gradually simpler structures through a path which eventually leads to simple or commercially available starting materials for a chemical synthesis.

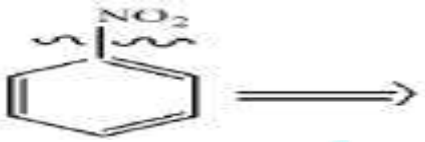


- **Disconnection:**

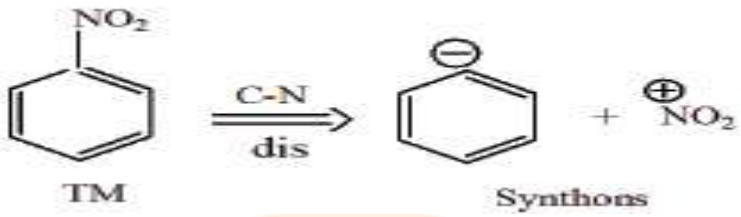
This term disconnection relates to breaking a carbon-carbon bond of molecule to generate shorter or simpler fragments.

In retrosynthesis, the reversal of a bond forming reaction *i.e.*, the cleavage of a bond to break the target molecule into possible starting materials is known as **disconnection.** The crucial step(s) in many syntheses is (are) bond formation. The reverse bond disconnection, while in planning a synthesis, helps to identify suitable synthetic routes. There is no general way to disconnect a molecule. Imaginary bond cleavage corresponding to the reverse of a forward reaction leading to the immediate precursor. This is also known as transformation and is indicated by a wavy line.

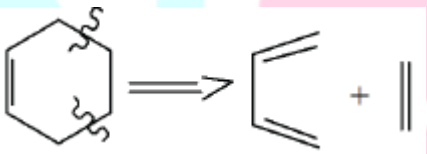
- **Retrosynthetic Arrow**: Disconnection is represented by a double line closed arrow which indicates the transformation of the molecule into its immediate precursor.



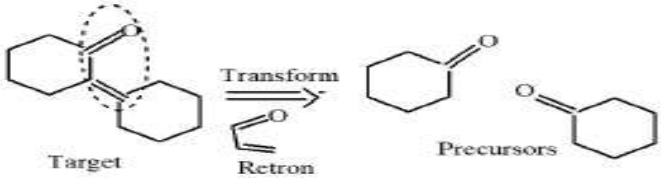
- **Synthons**: Synthons are the imaginary fragments obtained by disconnection. The concept of bond polarity with the fragments is of prime importance during disconnection. Synthons are not real compounds but are idealized ionic or neutral fragments, and they are not reagents. An idealized (often charged) molecular fragment is known as **Synthon**. Functionalized nucleophile can be denoted by d_n synthon, where, d represents the donor and n denotes the distance between FG and the reactive center. Functionalized electrophile is expressed as a synthon, where a is acceptor. Every retrosynthetic problem requires its individual creative solution. Experience and training are necessary traits for retrosynthetic analysis and planning of synthesis. The wider the span of knowledge of reactions and their scope someone knows, there more options for synthetic routes.



The following reaction shows a concerted cycloaddition reaction, where the synthons are neutral fragments.



- **Retron:** Each reaction generates a characteristic structural element in the product, such as the enone resulting from aldol condensation. This substructure, called the *retron*, must be present in a target molecule to be able to apply the corresponding transformation to that target.



- **Reagents**: These are the actual source of the synthons.

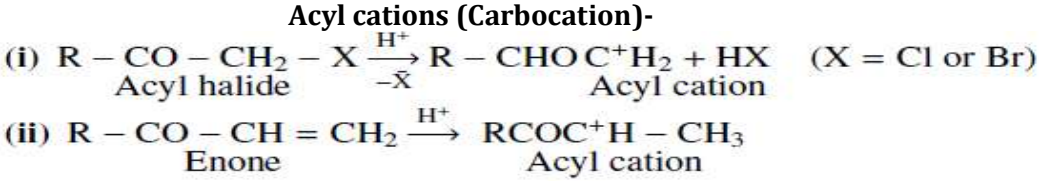
Alkyl anion (carbanion) –

$$R - M \longrightarrow \bar{R} + M^{+}$$

organometallic compound carbanion

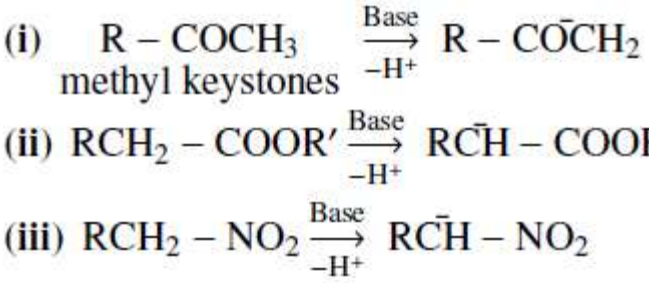
Acyl Ions:

Acyl cations (Carbocation)-



Acyl anion:

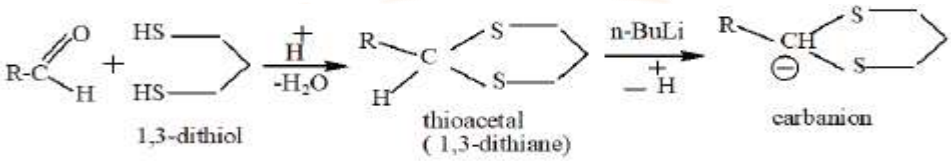
Removal of a proton from a methylene group adjacent to an electron withdrawing group



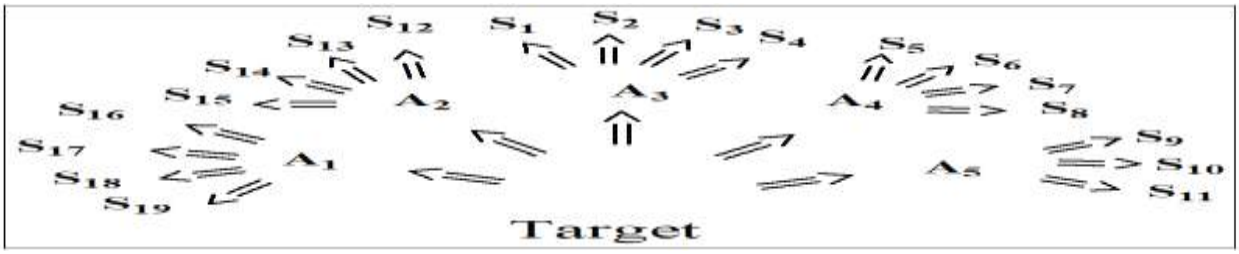
Aldehyde carbonyl as a cation and anion:

The aldehyde carbonyl carbon is electron deficient and undergoes nucleophilic attack.

The aldehyde carbonyl carbon can also undergo electrophilic attack when it is converted into an anion. The polarity of the electron – deficient aldehyde carbonyl carbon can be reversed and this is known as "umpolung"



- **Retrosynthetic tree:** It is a complex pattern of Retrosynthetic analysis of a molecule may lead to the possibility of identifying several different starting materials and several different routes to the synthesis of a molecule. several or all possible retrosynthesis of a single compound. Retrosynthetic analysis of a molecule may lead to the possibility of identifying several different starting materials and several different routes to the synthesis of a molecule. Each structure derived from a disconnection becomes a TM itself for further analysis. The analysis can be repeated for each precursor, generating a second level of precursors. Each precursor generated is checked for its availability. Such repeated disconnections give an outline of the available routes for the TM, and this is known as the retrosynthetic tree (*Figure* 1).



A retrosynthetic tree is a complex pattern with many branches which lead to different routes and different synthetic precursors. The synthetic tree is a graph of several synthetic routes to the TM which can be designed and evaluated, from which an efficient method is chosen. The synthetic plan is written by choosing an appropriate route according to the analysis and adding reagents and reaction conditions. The synthetic strategy was further simplified using computers.

Passive program: It is the use of computerized libraries which\ identify the structural features of the target molecule i.e., an aromatic ring, an acyclic ring, an alkyl group, etc. It is a collection of data from which we can locate all the compounds that contain a specified substructure corresponding to the TM. A huge collection of organic reactions is also available for use.

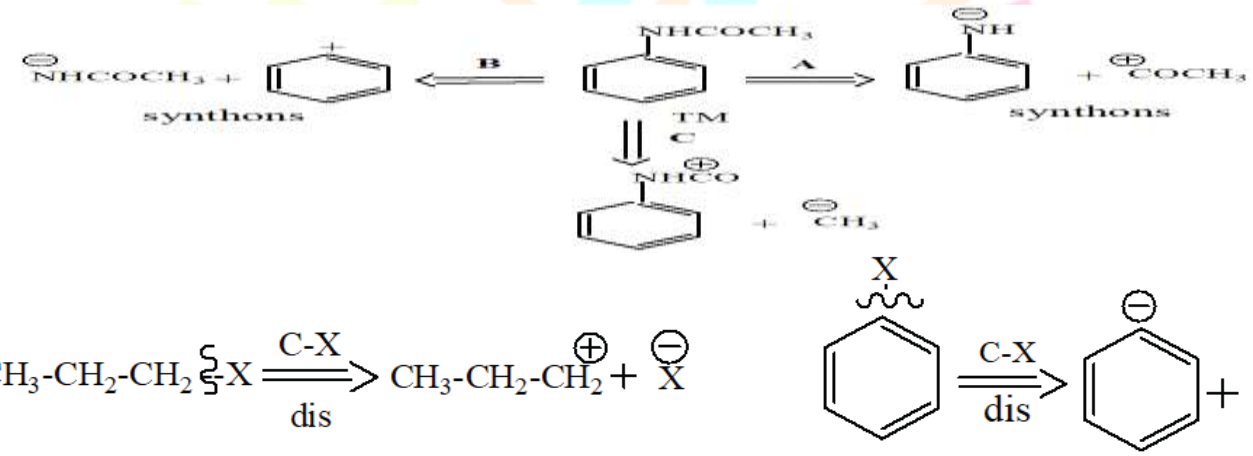
Active program*:* A menu is displayed with different strategies for retrosynthetic analysis

Guidelines or Empirical Rules (Heuristics) to a Proper Disconnection:

1) Disconnection should correspond to a known and reliable reaction. So, a thorough knowledge of reactions is necessary.

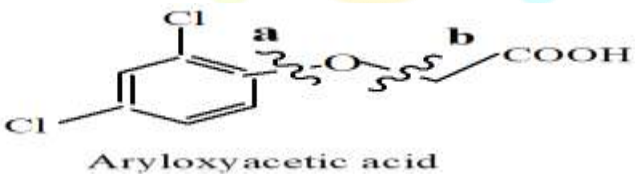
2) Disconnect C–X bond.

Figure 2. Route A is a good disconnection as acetylation of an amino group is a known reaction to get the N-acetyl group. Routes B and C route disconnections are improper as they do not lead to known reactions.

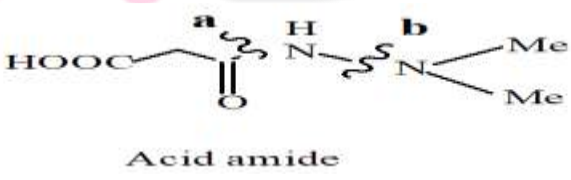


These are the known reactions where alkyl halides are obtained by nucleophilic attack by a halide whereas the halogen is an electrophile in the preparation of aryl halides.

3) For compounds comprising of two parts joined by a heteroatom, disconnection is carried out next to the heteroatom. The molecule is disconnected in the middle for greater simplification.



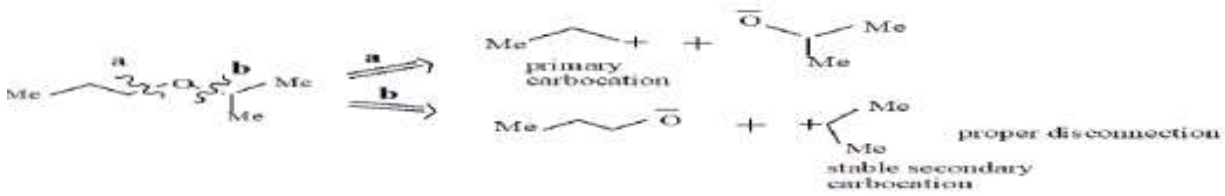
Aryloxyacetic acid



Acid amide

The aryloxy acetic acid can be readily obtained by reaction of a phenol and chloroacetic acid in presence of NaOH. So, the proper disconnection is at the ‘b’ site. The amide can be obtained from an acid chloride and an amine, so, the proper disconnection is at the site.

In open-chain compounds, the disconnection at the heteroatom is also based on the stability of the synthons. Both these disconnections are next to the heteroatom and in the middle to give equal size synthons. But route ‘a’ is preferred as it gives a more stable secondary cation.



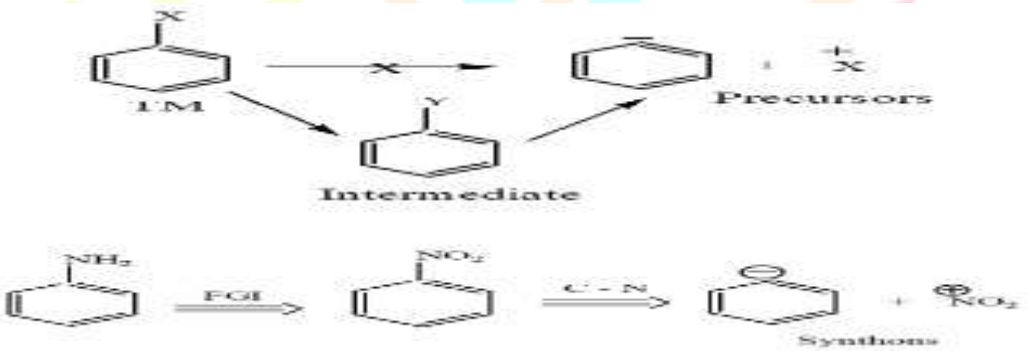
Group Oriented Strategy: Manipulation of the Functional

Groups

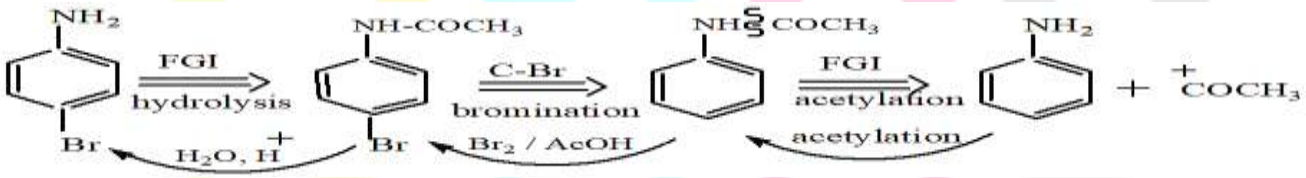
Whenever disconnection does not lead to reliable reactions, then the following changes must be carried out with the functional groups – FGI, FGA, FGR – and the unmasking of the latent functional groups by deprotection or other conversions. Manipulation of functional groups can lead to significant reductions in molecular complexity.

a) **Functional Group Interconversion (FGI):** FGI is substituting functional group for another when the disconnection of the group does not lead to a proper precursor. In the following reaction, disconnection is not possible because there is no corresponding reaction to introduce group X directly on the benzene ring. Hence, it must be converted to group Y by FGI as group Y can be disconnected to give the appropriate starting materials.

Aniline on bromination gives 2, 4, 6-tribromoaniline so the group interconversions must be carried. Amino group is readily obtained by the reduction of nitro group. So, in the above reaction, the first step is the functional group interconversion followed by disconnection.



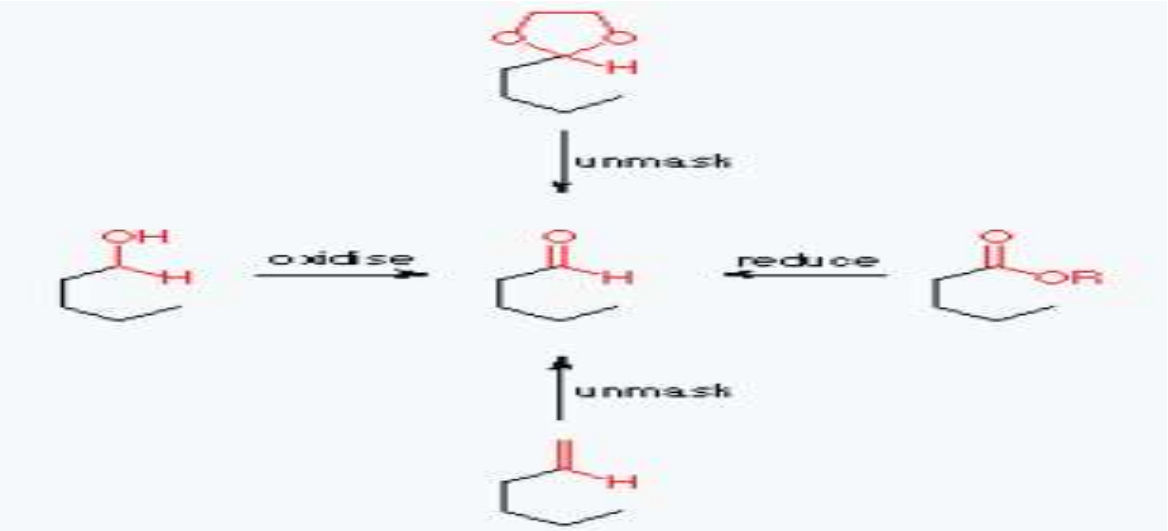
Preparation of p-bromoaniline from aniline is shown below



The synthetic route for the target molecule is the exact reverse of these retro steps.

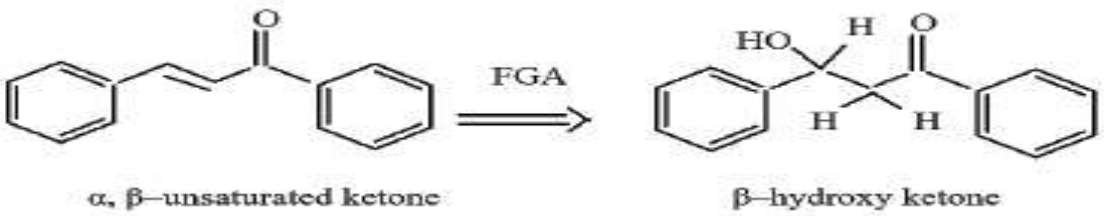
Many functional groups can be interconverted into each other**, *e.g.*, oxidation of an alcohol gives an aldehyde, and further oxidation gives carboxylic acid.** Many organic transformations can be used to do FGIs. Carbonyl groups are particularly useful in this respect. The reactivity of the carbonyl group can be masked during synthesis as double bond (ozonolysis for FGI into aldehyde) or dioxolane until needed.

Functional Group Interconversion (FGI)



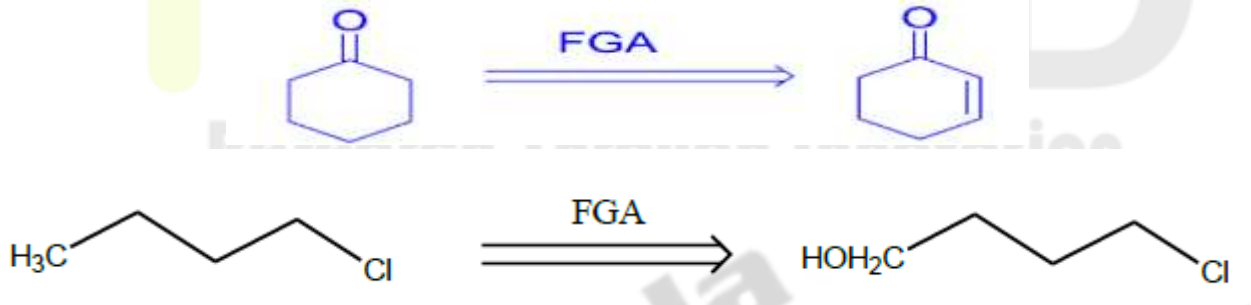
b) Functional Group Addition (FGA):

Some functional groups need the addition of a group to the immediate precursor suitable for disconnection. An example is the facile dehydration of β–hydroxy ketone that yields α, β–unsaturated ketone.



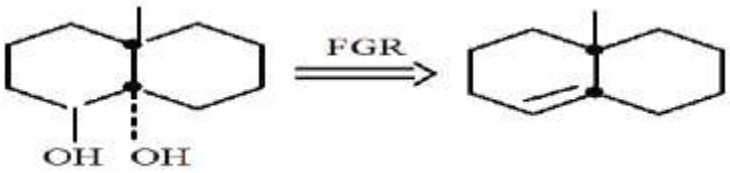
Retrosynthesis gives a "more" functionalized compound. The rationale of using FGA could be that the specific function is easier to make or that the specific function enables installation of other functional groups. As we can see here that the cyclohexanone is converted into cyclohex-2-enone using FGA. Here, we can see that the single functional group in cyclohexanone, i.e. carbonyl group gets converted by FGA to two functional groups, in cyclohex-2-enone. Alkene and carbonyl group. There is an additional of one functional group shows another example of FGA. Here, we can see that the hydroxyl functional group has been added to the existing chloro functional groups.

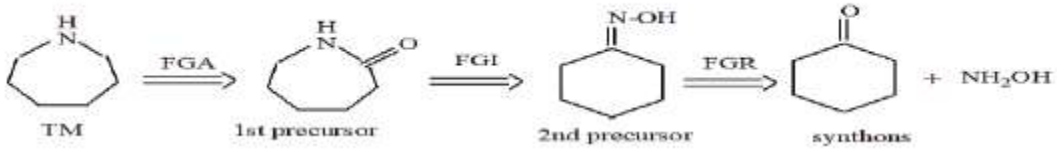
An example of Functional Group Addition (FGA)



c) Functional Group Removal (FGR):

A functional group must be removed to get a precursor required for the target molecule. In the following example, the precursor is a compound containing an olefinic double bond so the two hydroxyl groups are to be removed. The target molecule caprolactam is obtained by Beckmann rearrangement from the lactam. So, the first retro step is the addition of a keto group to obtain a lactam. This reaction involves both FGR and FGI.





. The alcoholic functional group is removed from the 6-hydroxycyclohex-2-enone to give us cyclohexanone, the removal of functional group, hydroxyl group.

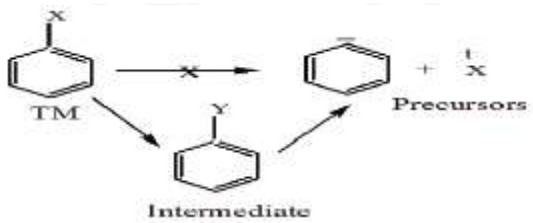
Box 1 shows the list of some common functional groups which cannot be introduced directly on the benzene ring and must undergo functional group inversion. However, simple compounds containing these groups which are commercially available can be used for the subsequent reactions.

Disconnection in Disubstituted Benzene Derivatives:

Disconnection in this substituted benzene derivatives is based on the relative positions of the groups, their reactivity and orientation. The order of events in the retrosynthetic analysis, based on the orientation and reactivity of the groups is illustrated by the following examples.

Box 1. Groups that have to undergo functional group inversion.

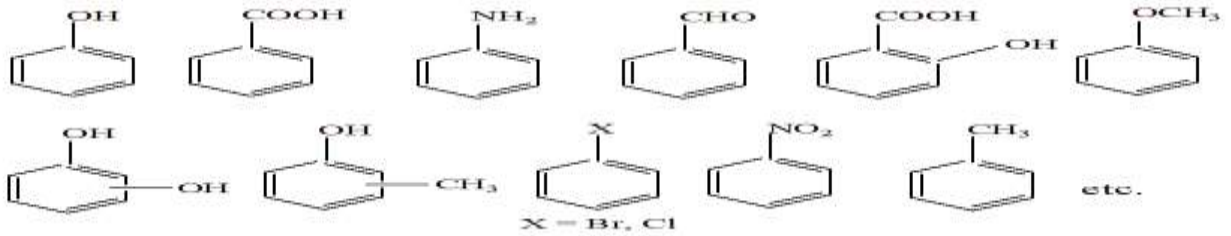
X	Y	Reaction	Reagent
$-NH_2$	$-NO_2$	Reduction	Sn / HCl
$-COOH_2$	$-CH_3$	Oxidation	$kMnO_4$, CrO_3, & H_2SO_4
	-CN	Hydrolysis	NaOH
-OH	$-NH_2$	Diazotisation	$NaNO_2$ + HCl & heating with H_3O^+
-OH	$-NH_2$	Diazotisation & heating with	$NaNO_2$ + HCl CuCN
-CN	$-NH_2$	Diazotisation & coupling with	$NaNO_2$ + HCl CuCN
-COCl	COOH	Reaction with	$SOCl_2$
$-CONH_2$	COCl	Reaction with	NH_3
-CHO	$-CH_2Cl$	Oxidation	Hexamine
-COOR	-COOH	Esterification	ROH & H^+



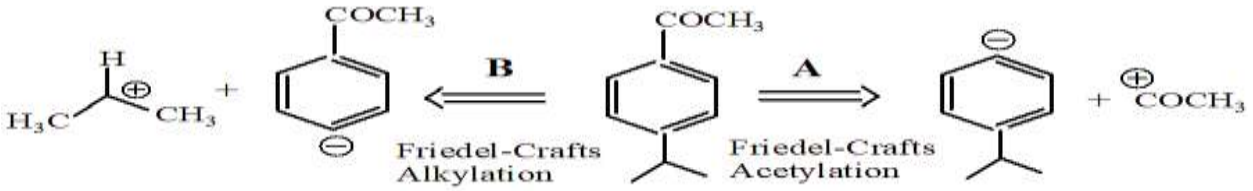
4–isopropyl acetophenone can be disconnected in two ways – A and B. Both, the acetyl, and the alkyl groups can be introduced by Friedel– Crafts reaction. The disconnection depends on the reactivity of the isopropyl and acetyl groups and their orientation for the incoming
group.

Disconnection B does not lead to proper precursors as the acetyl group deactivates the ring towards Friedel–Crafts alkylation reaction and it is a meta-orienting group.

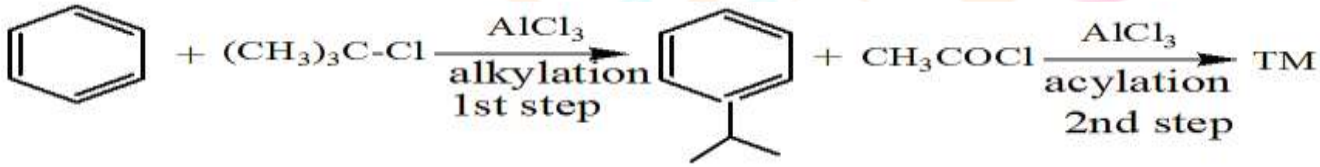
Disconnection A is a re- Alcohols can be treated liable reaction as central functional groups as they can be converted into various other functional groups. Alcohols are the starting materials for many functionalized aliphatic compounds. as the isopropyl group activates the ring towards.



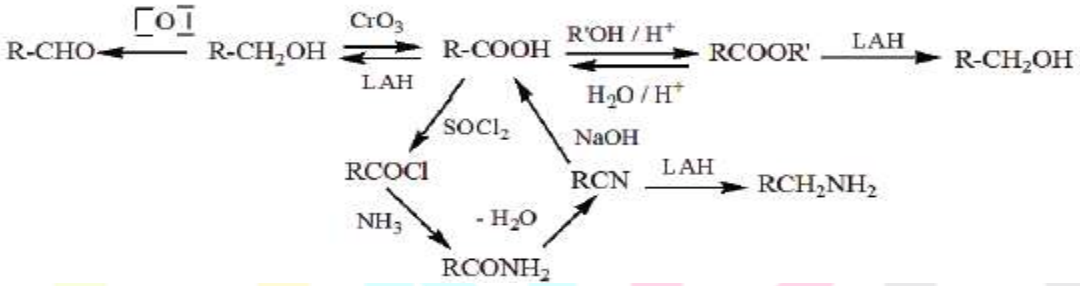
Friedel–Crafts reaction and is para-orientin:
The synthesis designed based on this retrosynthetic analysis is alkylation followed by acetylation.



Interconvertible Functional Groups:
The functional groups are easy to inter convert if the carbon skeleton remains unchanged. For e.g., the carboxylic group can be used to obtain various functional groups as follows:



Similarly, alcohols can be treated as central functional groups as they can be converted into various other functional groups. Alcohols are the starting materials for many functionalized aliphatic compounds.



Functional Group Transformation (FGT): This transformation involves the interchange of a functional group during retrosynthesis. Isomerization can be another term for the description of FGT.

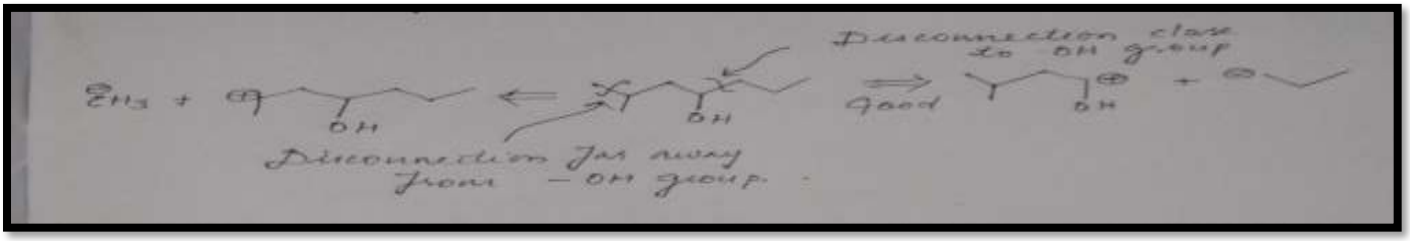
BASIC PRINCIPLE OF DISCONNECTIONS

RETROSYNTHETIC ANALYSIS:

- A disconnection is represented by a wavy (⦚) line through the bond being disconnected.
  - The complete set of disconnections and functional group interconversions for a specified target molecule is what constitutes a retrosynthetic pathway or plan.

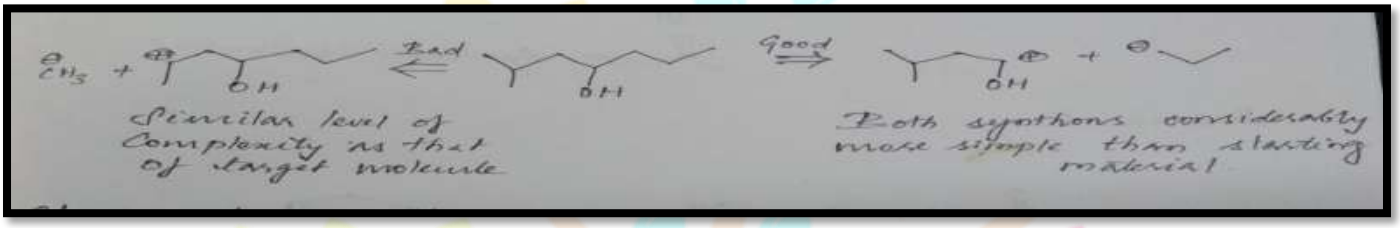
Position of disconnection:

Disconnections are very often taking place immediately adjacent to, or very close to functional groups in the target molecule (on being disconnected).



A good disconnection will simplified target molecule

- A good disconnection must achieve the greatest simplification of the target molecule. For a complex molecule, this basic disconnection process is repeated until the target is reduced to simple starting materials.

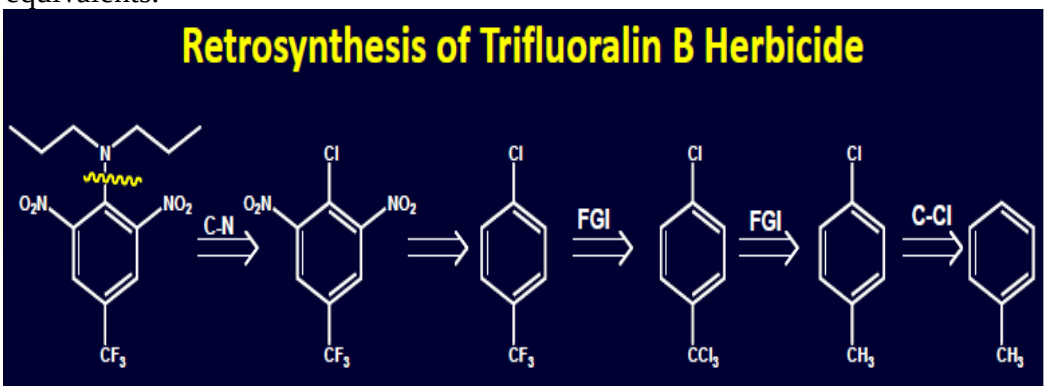


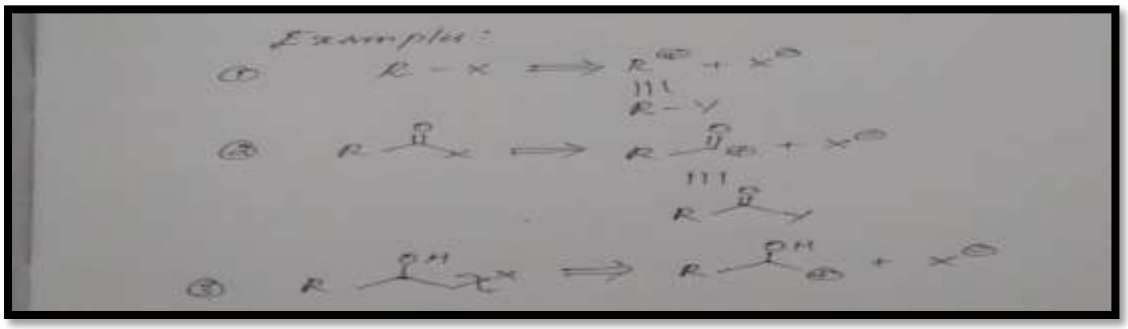
Charge of the synthon molecule:

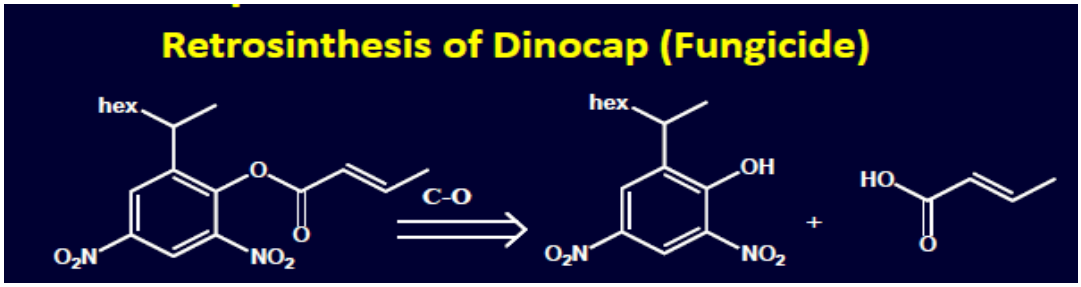
Consider whether the resonance structure can be drawn for the synthon which looks like a real reactive intermediate **MONOFUNCTIONAL DISCONNECTION:**

C-X Disconnections:

- In C-X disconnection a bond joining the hetero atom (X) to the rest of the molecule is disconnected: a C-O, C-N, C-S disconnection.
- The corresponding reactions are mostly nucleophilic displacement by SN1, SN2 or carbonyl substitution with amine, alcohol, and thiols on carbon electrophiles.
- It produces the carbo cationic synthon, and X-This is because the X is invariably more electronegative than carbon.
- C-X bond exists in different chemical environment, produce variety of carbo Cationic synthons and synthetic equivalents.

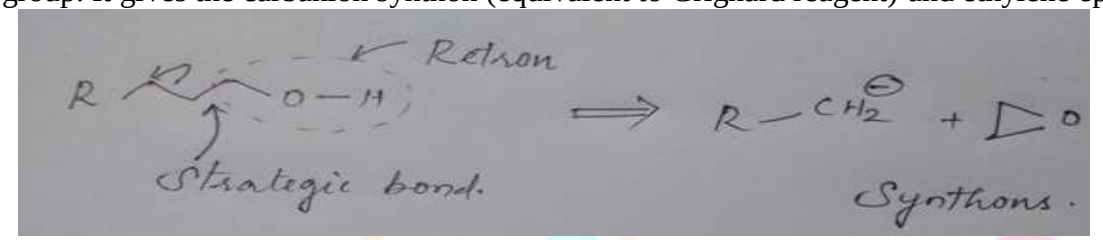






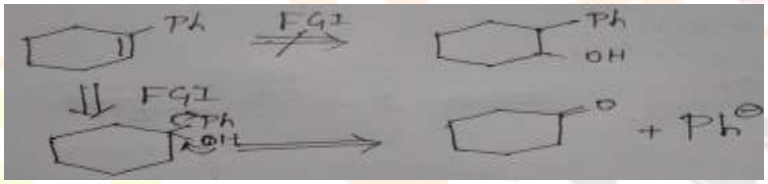
C-C Disconnections: (MONO –FUNCTIONAL GROUP)

Alcohol Disconnection: The primary alcohol, CH3-CH2-CH2-CH2-OH. The disconnection is done next to the hydroxyl
functional group. It gives the carbanion synthon (equivalent to Grignard reagent) and ethylene epoxide.

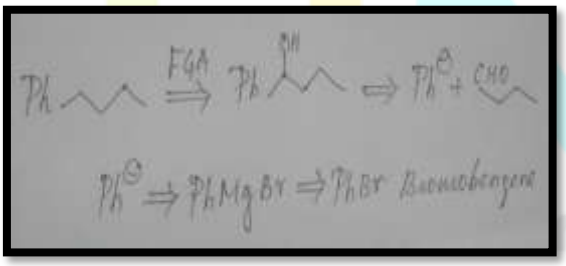


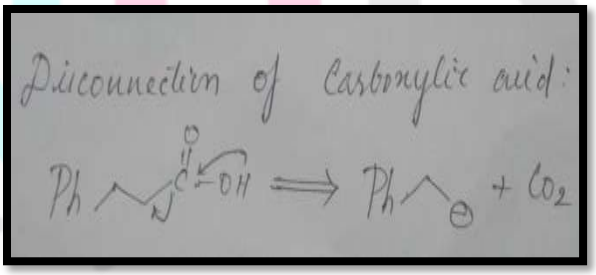
Alkenes disconnection: Connections of alkenes;

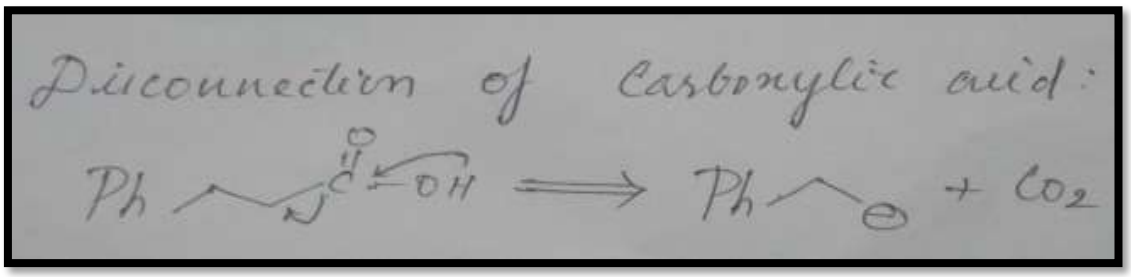
1. By functional group inter conversion of an alkene to an alcohol and then making alcohol disconnection.
2. By using witting transformation of C=C. (witting transformation is not available in case of C=C is a part of the ring)



- **DISCONNECTION CARBOXYLIC ACID:** The carboxylic acid is synthesized from hydrolysis of nitriles and the between Grignard reagent and carbon dioxide. So, in retro synthesis carboxylic acid disconnect to form carbanion and carbon dioxide.
- Carbanion is further disconnected into smaller synthons through the formation of Grignard reagent.
- **C=O Disconnection:** Methyl ketones are prepared by acetalization of ethyl acetoacetate.

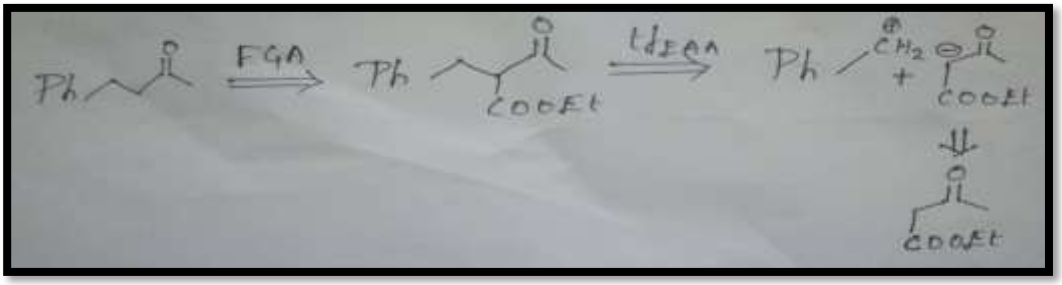






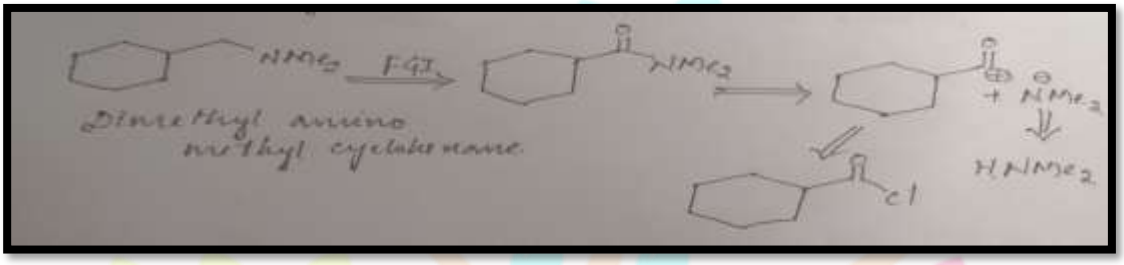
- **ALKANE DISCONNECTION:**

  In this example for (-OH) group is added closer to the ring, to get Phenyl- synthon.

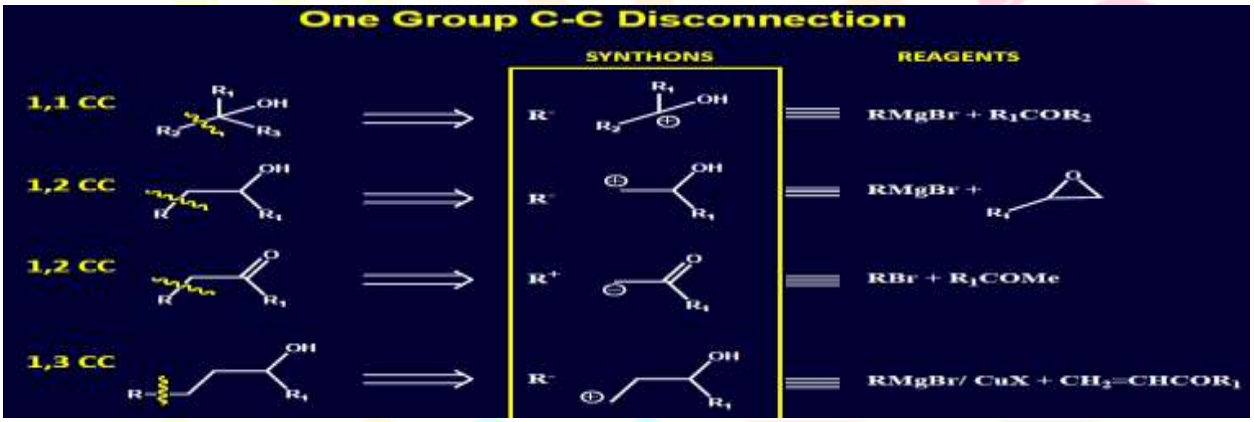


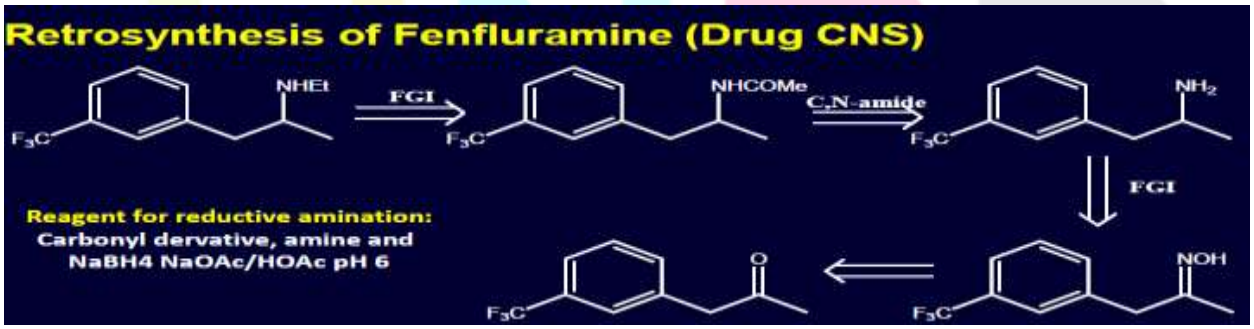
- **Amine disconnection**:

  A functional group inter conversion is performed to convert amine to amide and then disconnected. Because the primary amine on alkylation produces quaternary amine (over reactivity of the amine).



EXAMPLES:





BIFUNCTIONAL DISCONNECTION:

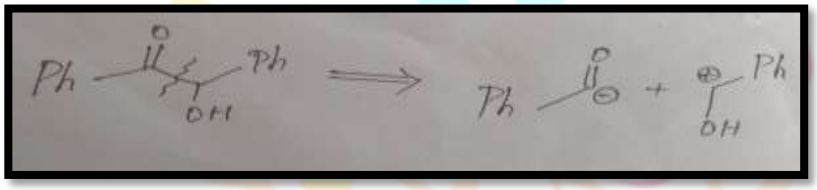
- Bi functional disconnections are classified according to the relative distances between the two functional groups under consideration. Example; 1,2-; 1,3-; 1,4-; 1,5-; and 1,6- di functional disconnections.

- Alcoholic –OH group can be possibly be converted to any other functional groups, so these bi functional disconnections are described for oxygen containing functional group only. Indirectly it is also applicable to other bi functional compounds.

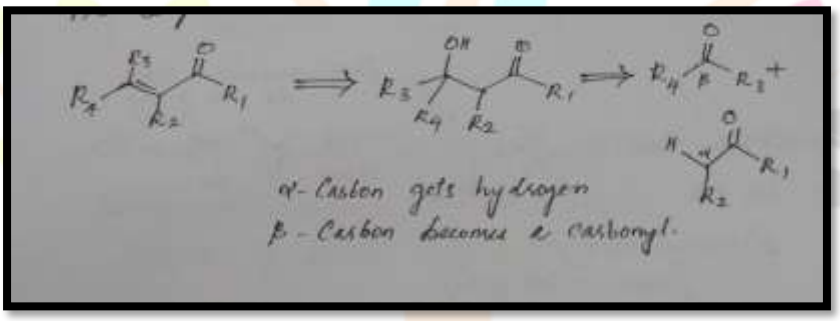
- So, these compounds are abbreviated as 1,2 – di O- disconnection,1,5-di O- disconnection etc.
- On these bi-functional disconnection, 1,3-di O, 1,5-di O, 1,6-di O disconnections are quite convenient.
- **1,2 DIFUNCTIONAL DISCONNECTIONS:**

EXAMPLES:
1,2- DIOLS: 1,2- diols are disconnected through functional group inter conversion into alkene.

α – hydroxyl ketones via benzoin condensation

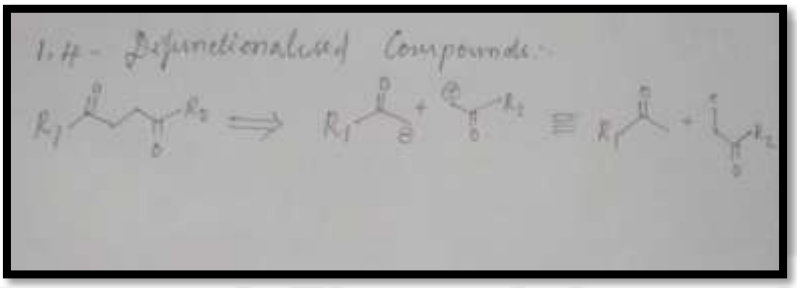


1, 3- Difunctional disconnection: Aldols undergo 1,3- difunctional disconnection



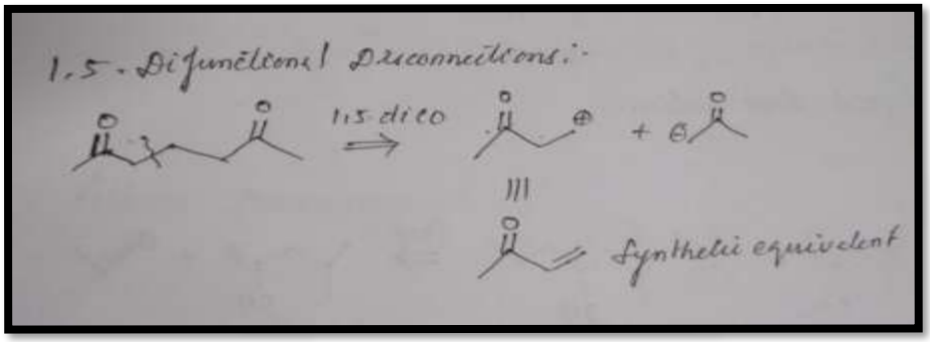
1,4 DIFUNCTIONAL DISCONNECTIONS:

1,4- DIKETO COMPOUNDS



1,5 DIFUNCTIONAL DISCONECTIONS:

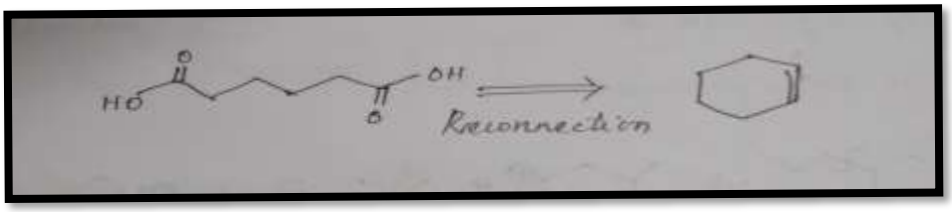
1,5- di-O- disconnections is since Michael addition of a carbanion to an α, β- unsaturated carbonyl Michael addition. Here is Michael addition transform.

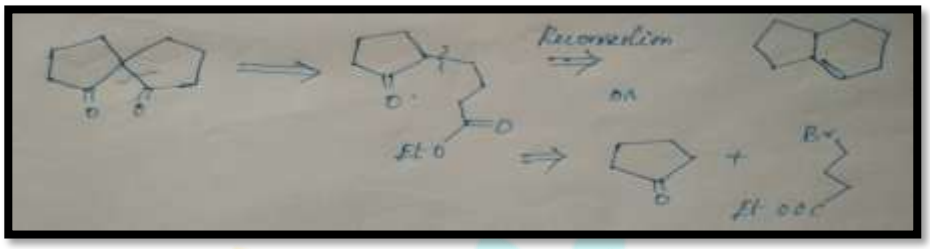


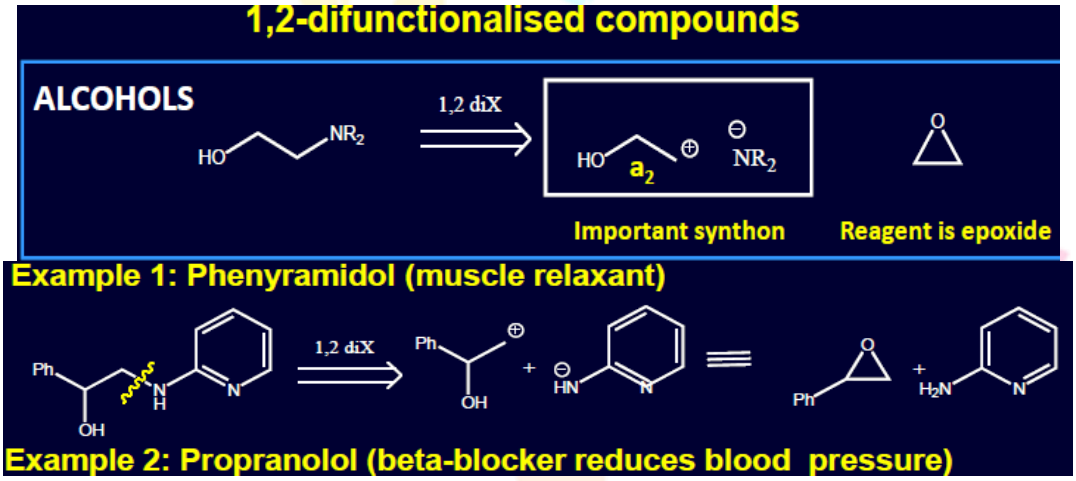
1,6-DIFUCTIONAL DISCONNECTION:

"Reconnection" is a reliable strategy for synthesizing

1,6 –di functionalized compounds since the cyclohexenes required for the oxidative are easily accessible.



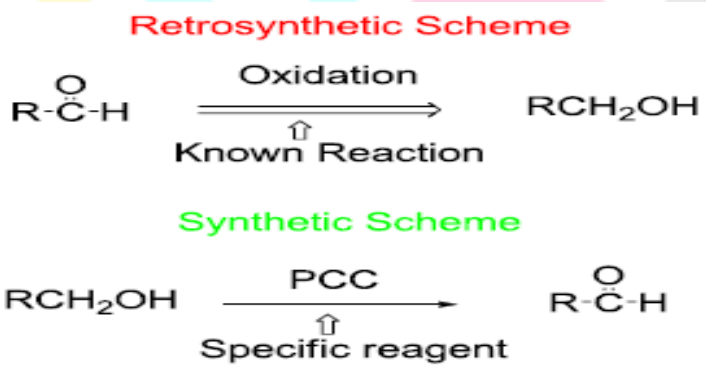




Synthetic Planning

Definition

Synthesis is a construction process that involves converting simple or commercially available molecules into complex molecules using specific reagents associated with known reactions in the retrosynthetic scheme.



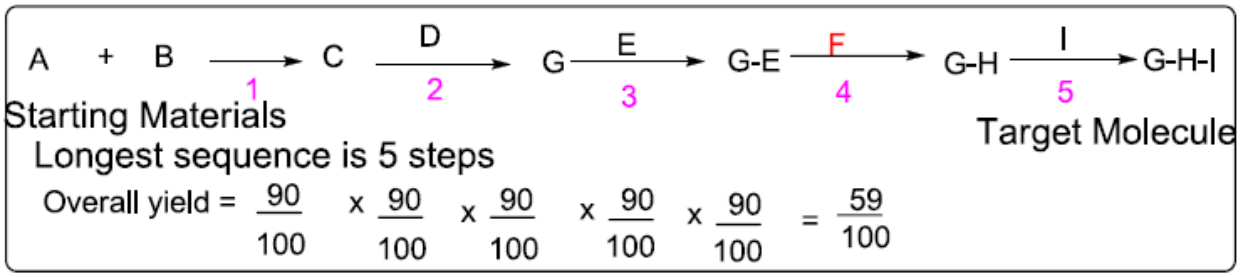
TYPES OF SYNTHESIS: (Retro-Synthesis)

A) Linear synthesis: Building up of molecule takes place step by step from simple **Starting Material** (TM to SM)- Sequence Reaction.

In linear synthesis, the target molecule is synthesized through a series of linear transformations.

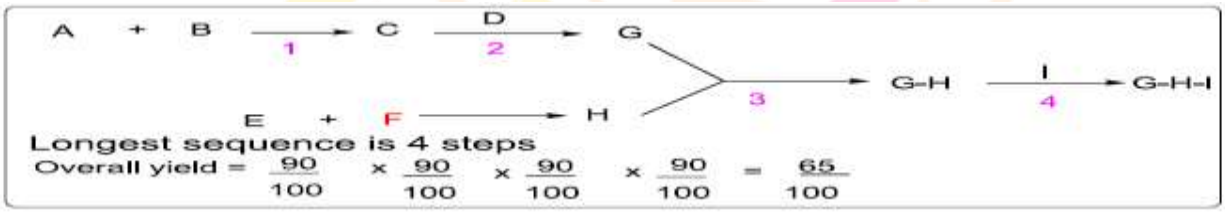
Since the overall yield of the synthesis is based on the single longest route to the target molecule, by being long, a linear synthesis suffers a lower overall yield.

The linear synthesis is fraught with failure for its lack of flexibility leading to potential large losses in the material already invested in the synthesis at the time of failure.



B) Convergent synthesis: Two parts of the molecule are synthesized separately and are joined by suitable reaction to get **Target Molecule.**

In convergent synthesis, key fragments of the target molecule are synthesized separately or independently and then brought together at a later stage in the synthesis to make the target molecule.



A convergent synthesis is shorter and more efficient than a linear synthesis leading to a higher overall yield.

It is flexible and easier to execute due to the independent synthesis of the fragments of the target molecule.

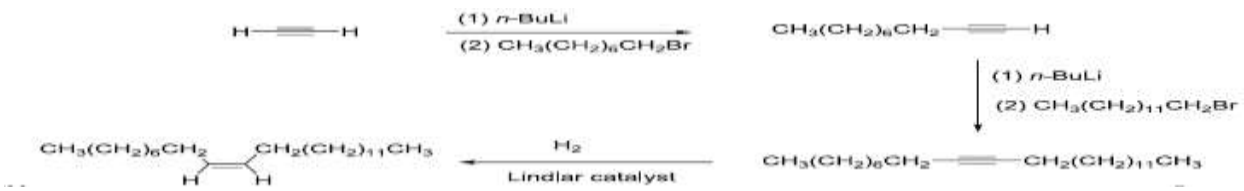
Synthetic Planning

Retrosynthetic analysis and synthetic planning require training (knowledge of chemistry) and experience (practical application of the chemistry).

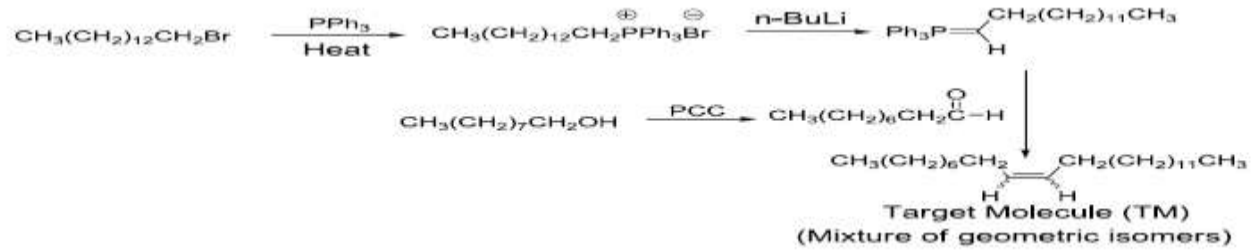
The wider someone's knowledgebase is in organic chemistry, the more the options available to one to develop a variety of synthetic routes to a target molecule. One of these retrosynthetic pathways may turn out to be more practical and executable than the others.

A good synthetic plan should consider considering the advantage of a convergent synthesis, if possible, over a linear synthesis.

When evaluating the various retrosynthetic schemes of the target molecule, it is important to recognize the strategic features of the molecule that the synthesis must address. Consider the chemical syntheses of Musca lure to appreciate how the two retrosynthetic plans fit in, but most importantly, note the use of specific reagents that transform the intermediates in the retrosynthetic scheme eventually to the target molecule.

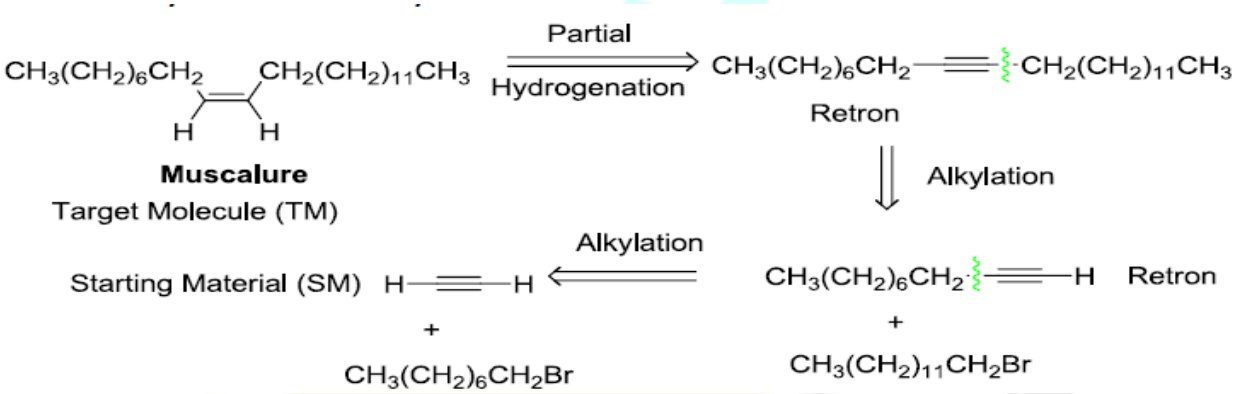


Synthesis of Musca lure via the Wittig reaction:



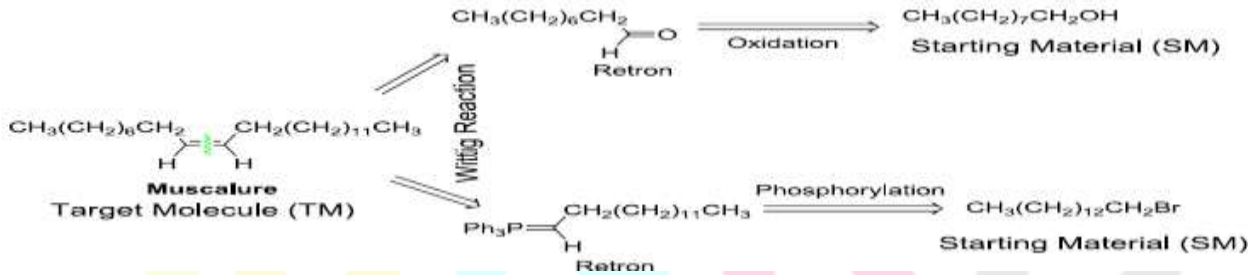
Comparing the two synthetic pathways shows that while the Wittig route is convergent, the stereochemistry of the double bond is not stereo specifically controlled.
The linear pathway of the stereospecific partial reduction of a terminal alkyne is the preferred route to Muscular.

Retrosynthetic For Muscular



The retrosynthetic analysis of any target molecule must be based on known chemical reaction for it to stand a realistic chance of being translated to a chemical synthesis.

Muscular can also be deconstructed based on the Wittig reaction.



A thorough evaluation of the alternative retrosynthetic pathways should be made to identify the pathway that best stands a realistic chance of being translated to an efficient chemical synthesis.

Strategies in Synthetic Planning

(a) Strive for success and good cost management

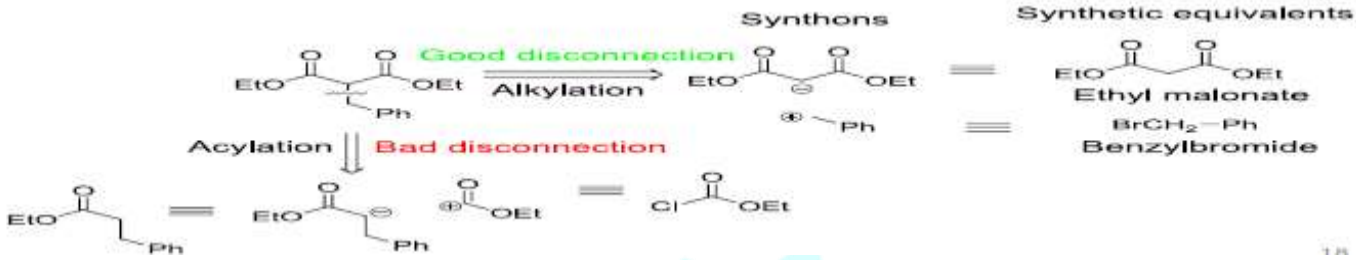
In planning a synthesis generate many retrosynthetic pathways to the target molecule: Examine these retrosynthetic pathways to identify among them an optimal synthetic route for which reagents are readily available and inexpensive.

(b) Convergent vs Linear synthesis

When considering a disconnection in the retrosynthetic analysis of a complex target molecule, try (if possible) to divide the molecule into halves at convenient bonds. This will make possible the formulation of a convergent synthesis with several mini-syntheses leading to the target molecule.

(c) Aim for disconnections that lead to the greatest simplification of the target molecule:

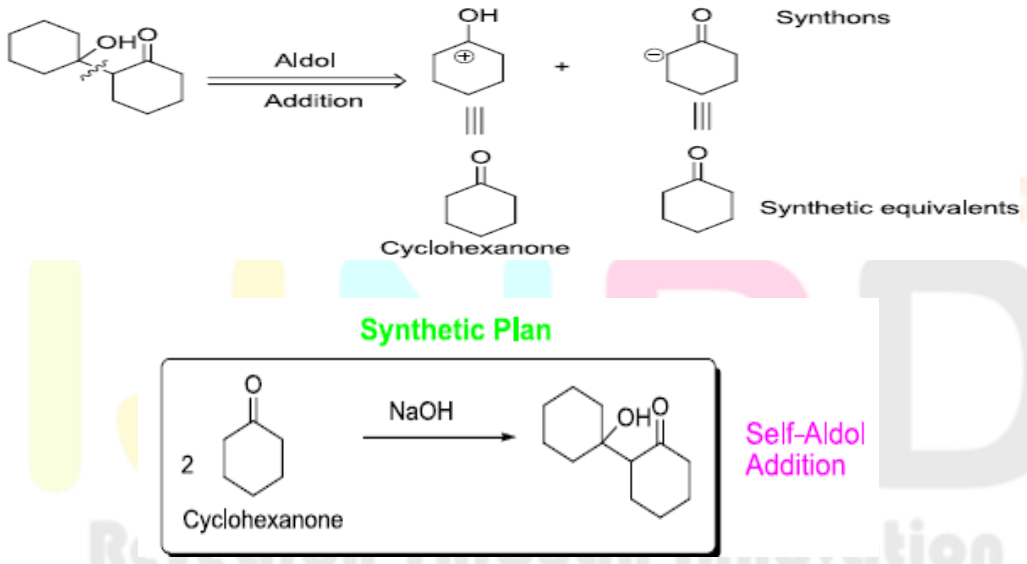
Given a choice of possible disconnections, those located at branch points or on rings are more strategic as they usually give straight chain fragments which are more likely to be commercially available or simply prepared.



(d) Identify and exploit any inherent symmetry in a target molecule:

Exploiting any symmetry in a TM or its intermediate can dramatically simplify its retrosynthesis. This may also provide an opportunity to identify a convergent pathway in the synthesis.

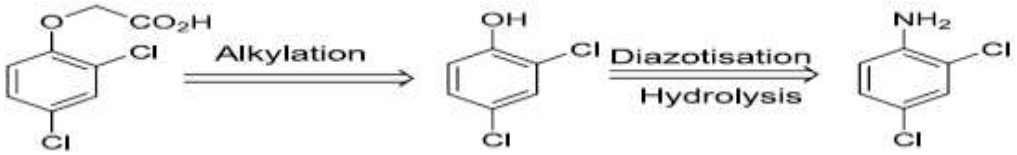
Retrosynthetic Plan:



(e) Introduce reactive functional groups at a late stage in the synthesis:

It is often difficult to selectively react at a less reactive functional group when a more reactive functionality is present within the same molecule. Such reactive functional groups are usually among the first to be disconnected during retrosynthetic analysis. The retrosynthetic analysis of 2,4-dichlorophenoxyacetic acid (2,4-D), a common herbicide for the control of broad-leafed weeds, is shown below:

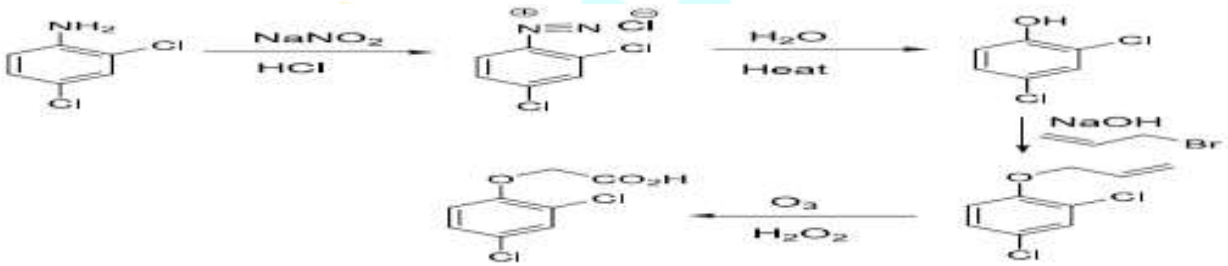
Retro Synthetic Plan:



2,4-dichlorophenoxyacetic acid 2,4-dichlorophenol 2,4-dichloroaniline

Synthesis of the Weed-Killer, 2,4-Disconnection:

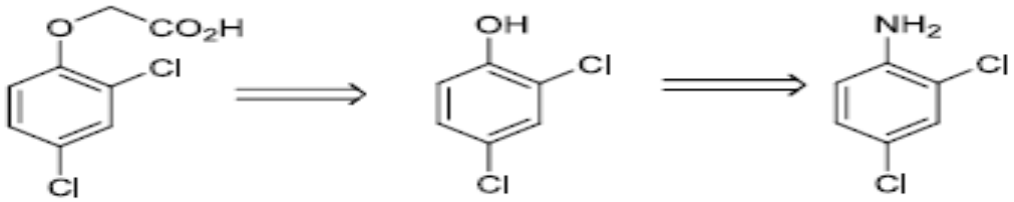
Based on the preceding retrosynthetic plan, 2,4- dichlorophene acetic acid (2,4-D) can be synthesized as shown below:



Alternative Synthesis of the Weed-Killer, 2,4-D (2,4-dichlorophenoxyacetic acid)

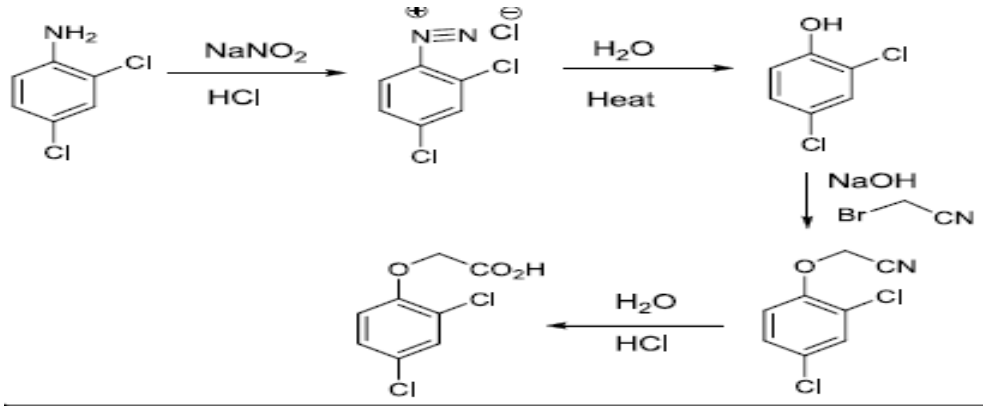
The synthesis of 2,4-Disconnection can also be approached based on the alternative retrosynthetic and synthetic plan highlighted below.

Retrosynthesis Plan



2,4-D

Synthetic Plan



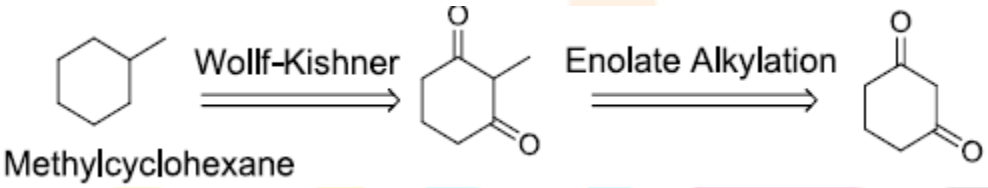
(f) During retrosynthetic analysis introduce additional functional groups, if necessary, to facilitate further disconnection: Functional group addition (FGA) strategy:

The functional group addition strategy in retrosynthetic analysis involves introducing additional functional groups at strategic locations in a retro, if necessary, to guide further disconnections based on known powerful bond making reactions.
Addition of functional groups e.g. double bonds or carbonyl groups can serve to direct reactivity to specific sites of a molecule significantly simplifying a synthesis.

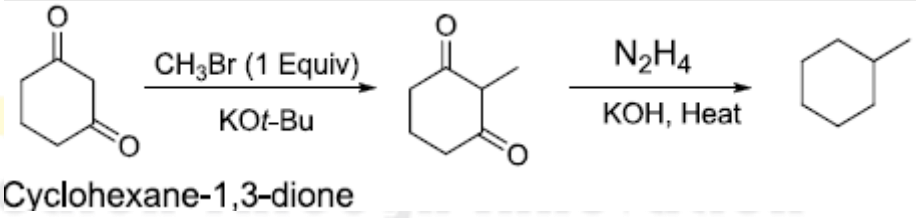
Functional Group Addition Strategy:

For example, one may introduce a carbonyl group in a substituted cyclohexane target molecule which may help guide introduction of a substituent through enolate alkylation.

Retrosynthetic Plan:



Synthetic Plan:

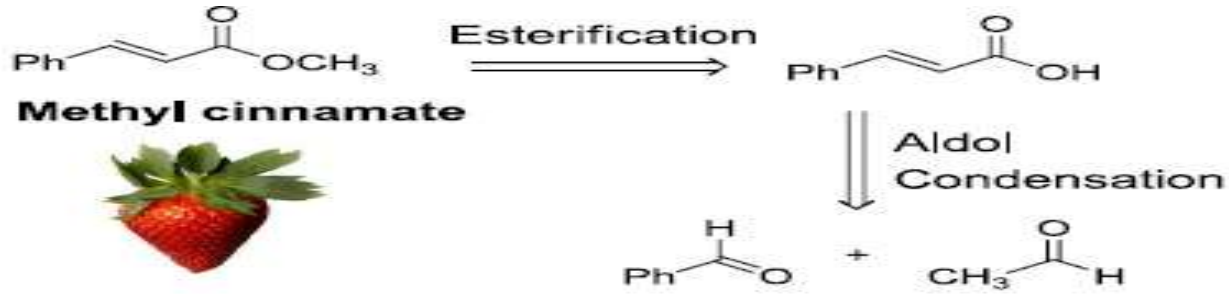


Application for Retrosynthesis and Synthetic Route:

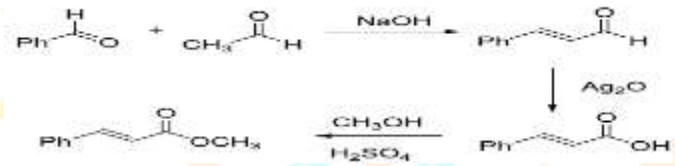
1) Retrosynthetic Analysis of Methyl Cinnamate:

Methyl cinnamate is found naturally in fruits, like strawberry. It is used in the flavor and perfume industries.

RETROSYNTHETIC PLAN:



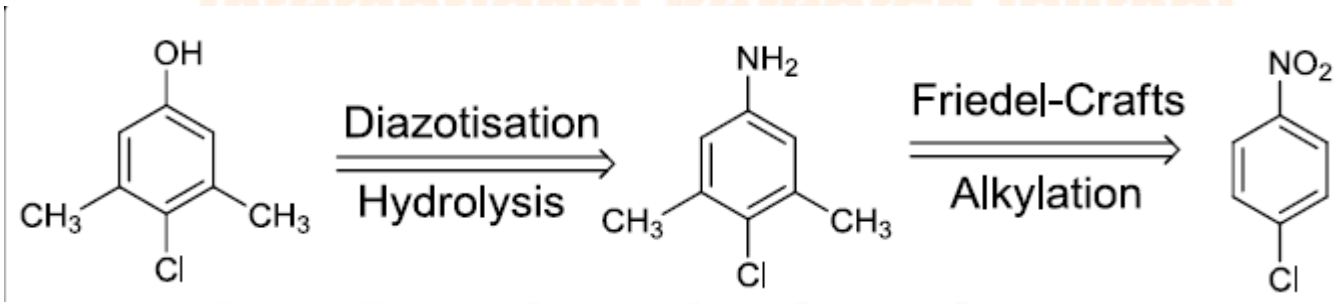
SYNTHETIC PLAN:



2) Retrosynthetic Analysis of Dettol:

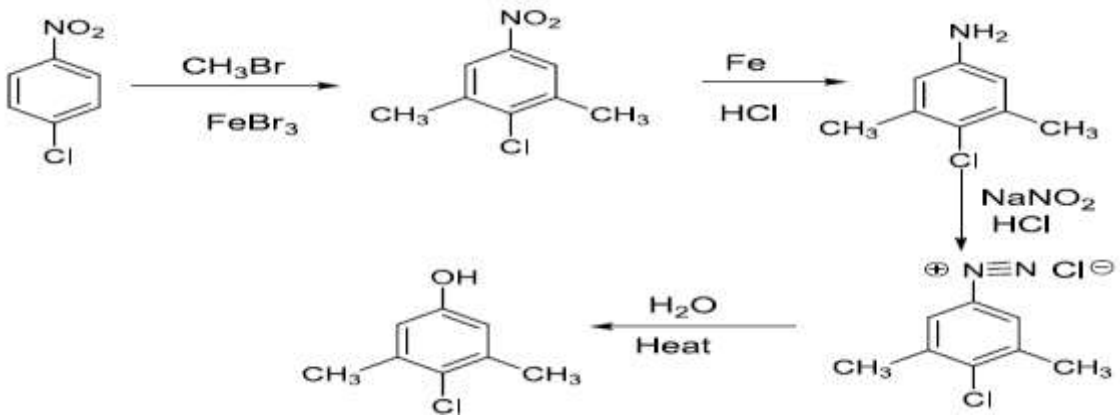
4-Chloro-3,5-dimethylphenol is the active ingredient responsible for the antiseptic properties of Dettol. The retrosynthetic analysis of Dettol from 4-chloronitrobenzene is outlined below.

RETROSYNTHETIC PLAN



Synthesis of Dettol:

The synthesis of Dettol from 4-chloronitrobenzene is outlined below:



3) Retrosynthetic Analysis of Z-Hex-2-enal:

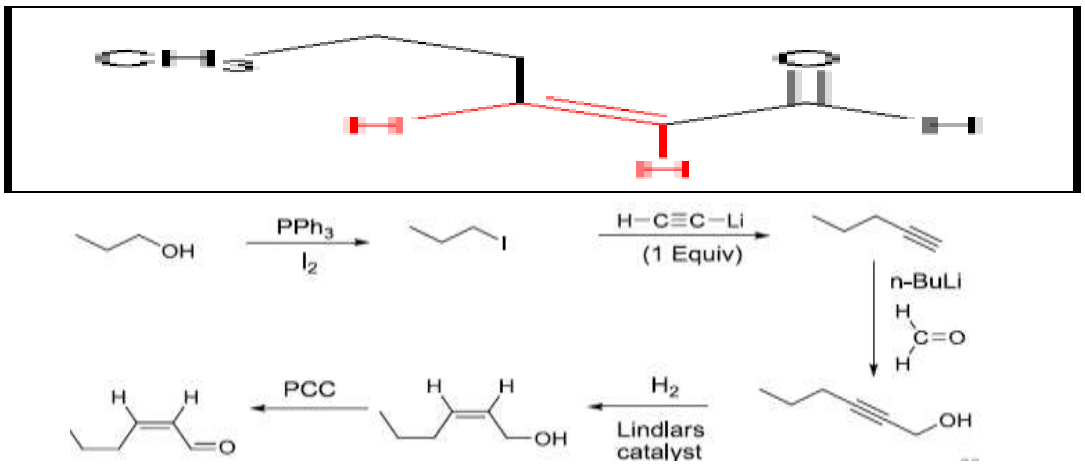
Z-Hex-2-enal provides the aroma reminiscent of cabbages, but has also found application as an insect repellent.

The synthesis of Z-hex-2-enal can be approached based on partial syn-hydrogenation as shown below:

RETROSYNTHETIC PLAN:

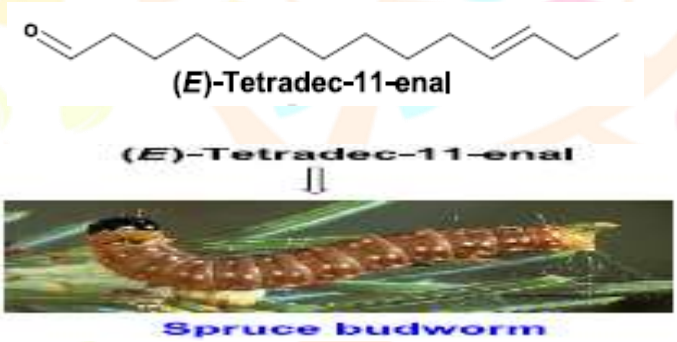
Synthesis of Z-Hex-2-enal:

The key feature in the synthesis of Z-hex-2-enal is stereochemistry of the double bond that can stereo specifically be achieved by partial syn-hydrogenation of an alkyne.



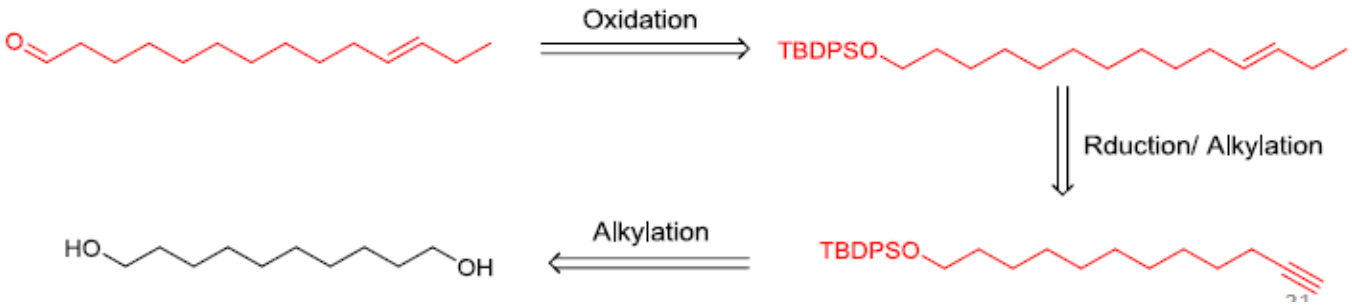
4) **Retrosynthetic Analysis of(E)-Tetradec-11-enal**

(E)-Tetradec-11-enal is the pheromone of the spruce budworm



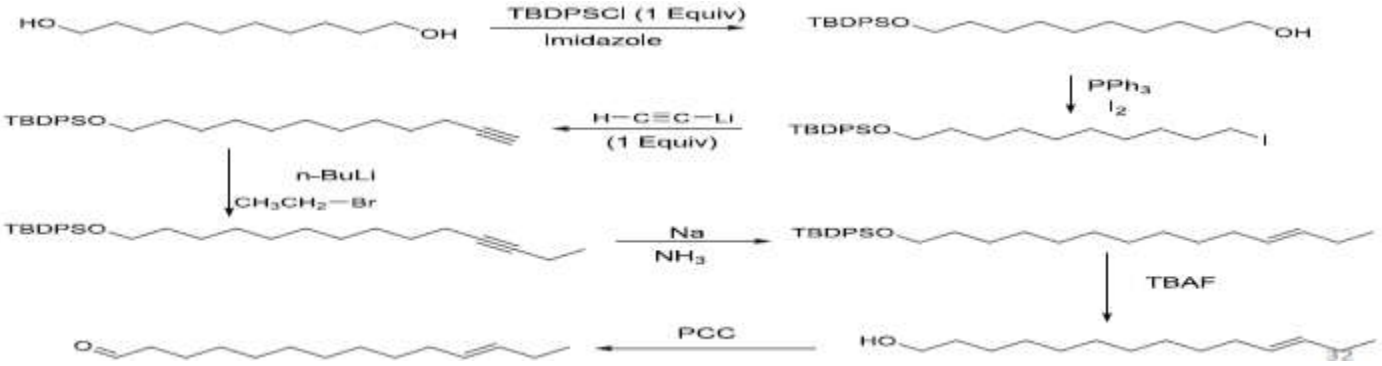
The synthesis of (E)-tetradec-11-enal can be approached based on partial trans-hydrogenation as shown below:

RETROSYNTHETIC PLAN:

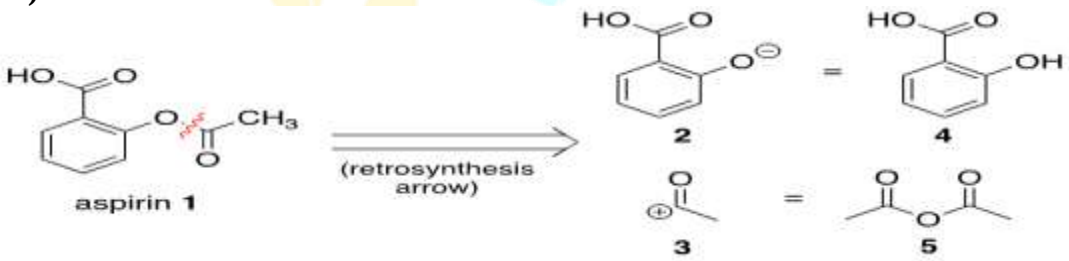


Synthesis of (E)-Tetradec-11-enal:

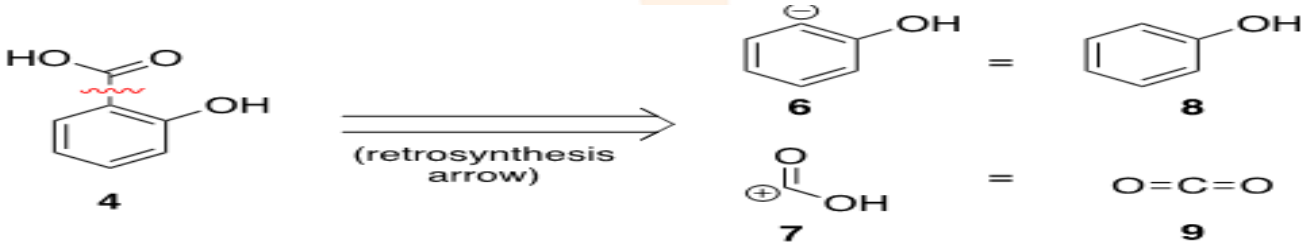
The synthesis of (E)-tetradec-11-enal must address the stereospecific synthesis of the E-double bond and ensure that the reactive aldehyde group is generated last.



5) RETROSYNTHESIS FOR ASPIRIN:

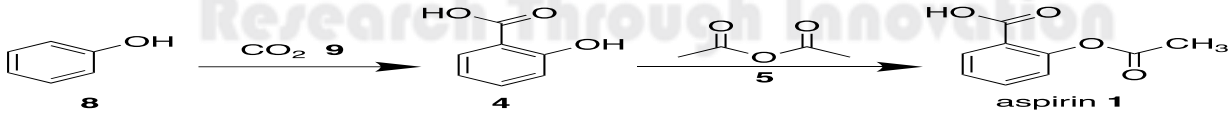


As shown in the first diagram, aspirin **1** can be chopped up into synthons**2** and **3**. One question here is why break the bond in the position shown. The answer is if the bond is broken here the equivalent molecules **4** and **5** can react together through a simple nucleophilic addition-elimination reaction. But for instance, molecule **5**(ethanoic anhydride) could be a range of electrophiles which react to add acetyl group to a molecule.



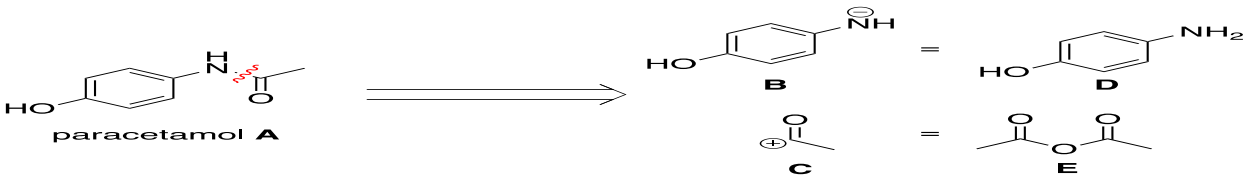
As shown in the second diagram, Salicylic acid**4** can be chopped up further into synthons **6** and **7**. One big question here is why have the charges on the synthons that way around. The answer is if the charges are this way around, it is possible to react the equivalent molecules **8**and **9** together through electrophilic substitution. Al so if the charges on synthons **6** and **7** were the other way around, it would make little sense chemically, as it is highly unlikely an electron rich benzene ring would act as an electrophile.

SYNTHESIS OF ASPIRIN:

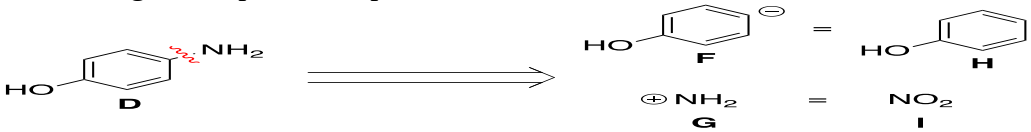


To summaries aspirin can be taken back to common chemical starting materials, ethanoic anhydride **5**, phenol **8** and CO_2**9**. Therefore, the forward synthesis would be this;

6) RETROSYNTHESIS FOR PARACETAMOL:

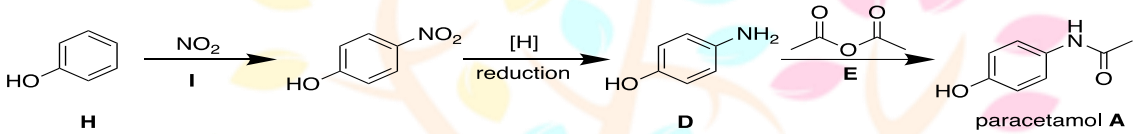


As shown in the paracetamol **A** can be chopped up into synthons **B** and **C**. One question here is why break the bond in the position shown. The answer is if the bond is broken here the equivalent molecules **D** and **E** can react together through a simple nucleophilic addition-elimination reaction as before.



As shown in the molecule **D** can be chopped (Backward) up further into synthons **F** and **G**. One big question here is why has NO_2 appeared? The answer is that NH_2 is a poor electrophile (it usually acts as a nucleophile!). Therefore, an equivalent electrophile for NH_2 would be NO_2 which can then be reduced to NH_2.Thus NO_2 can react with phenol (molecule **H**) through electrophilic substitution.

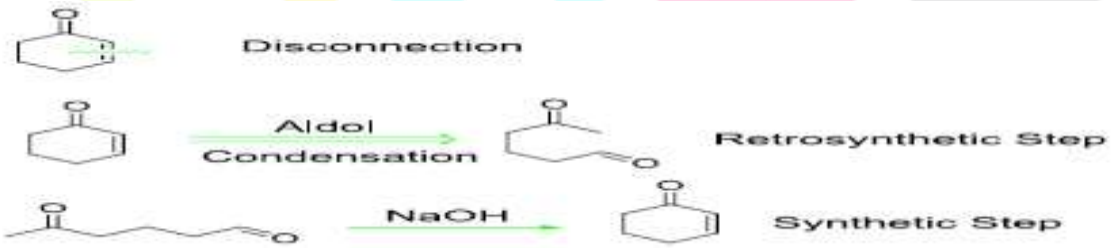
SYNTHESIS FOR PARACETAMOL:



To summaries paracetamol can be taken back to common chemical starting materials, ethanoic anhydride **E**, phenol **H** and NO_2**I**. Therefore, forward synthesis would be this;

Symbols of Retrosynthetic Analysis

- A disconnection is represented by a wavy ( ) line through the bond being disconnected.
- A retrosynthetic arrow (⇒): A retrosynthetic arrow is used to show retrosynthesis is taking place though the breaking of a bond and NOT a reaction. The retrosynthesis arrow allows a clear distinction between a reaction taking place and retrosynthetic analysis. This open arrow represents going from the target molecule "backwards" to simpler molecules (retros).
- A synthetic arrow (⟶): This closed arrow represents going in the forward direction.



Tips for Synthesis Based on Retrosynthetic Analysis:

An efficient synthesis should be planned based on the following conditions:

• Advantages and disadvantages of the route. • Availability of the starting materials for each step.
• Type of reactions: Less competent reactions should be involved in the synthesis. The reaction conditions should be simple and high yielding processes. They should work out on industrial scale. Yield at each step is to be considered.

• **Safety**: Dangerous chemicals are best avoided when planning a synthesis as they require more expensive equipment to ensure safe handling and containment. More important is they pose more danger to the person handling them. This is an important consideration for large scale preparations.

• **Length and cost of each synthetic step**: Minimum number of steps would save time. A convergent synthesis is preferred over the linear method. A lengthy scheme can be selected when the starting materials are inexpensive and readily available and easy experimental conditions are involved. Expensive starting materials are used when the number of steps is less.

• **Starting materials for industrial syntheses:** Starting compounds of linear skeleton up to six carbon atoms with one functional group like – COOH, CHO, OH, X, NH2, etc., are commercially available. Small molecules like simple aromatic compounds, alkenes, monomers for plastics, etc., are commercially available. Naturally occurring compounds like amino acids, simple sugars and other plant materials are preferred.

NOTES: FGA- Stability of the (SM) –for the essential FG- is Addition of Groups Is (Benzoic **Acid** (SM) – FGA-[Methylation]- Benzoate (SM)-**Ester)**

1) DIS/CONNECTION- **(TM to SM), Structure-Elucidation-Reaction, To Produced-Charged Particles, Reagents, C+, C-.**
2) **Bond broken from to Charge Particles (Nucleofission-Reaction), Reversible-Reactions, Innovation to Precursors.**

SIGNIFICANCE:

1) **To identify (SM)-lead/precursor- Organic Synthetic Compounds.**
2) **To Determine Optimum Synthetic Rote –Choosing.**
3) **To Aid of Structure Elucidation Reactions.**
4) **To Avoid Intermediate Compound interference (Sequence –Reaction)**
5) **To useful for the Natural Compounds to Synthetic –Compound (Derivatives)**

Summary:

Retrosynthetic analysis (retrosynthesis) is a technique for planning a synthesis, especially of complex organic molecules, whereby the complex target molecule (TM) is reduced into a sequence of progressively simpler structures along a pathway which ultimately leads to the identification of a simple or commercially available starting material (SM) from which a chemical synthesis can then be developed. Retrosynthetic analysis is based on known reactions (e.g the Wittig reaction, oxidation, reduction etc).

The synthetic plan generated from the retro synthetic analysis will be the roadmap to guide the synthesis of the target molecule.

CONCLUSION:

Retrosynthesis is a technique chemists use to identify how to synthesized a molecule through approaching the problem backwards. Effectively retrosynthesis starts from the wanted product and works backwards chopping and changing the molecule into smaller pieces to identify what the previous molecule can be made from.

It is the art of planning organic synthesis by transforming the structure of the desired molecule to simple commercially available starting materials for its synthesis. The aim of Retrosynthetic analysis to not only simplify but also aid the discovery of new synthetic routes and compare them for the development of an efficient synthetic strategy for a complex organic molecule.

ACKNOLEDGEMENT:

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