CHEMISTRY HONOURS

SEMESTER-4

CEMA-CC-4-8-TH: ORGANIC CHEMISTRY-4

TOPIC: THE LOGIC OF ORGANIC SYNTHESIS

MODULE-1

Contents: ***Retrosynthetic analysis:disconnections:***

- **(i)** Synthons, donor and acceptor synthons
- **(ii)** Natural reactivity and umpolung
- **(iii)** Latent polarity in bifunctional compounds:
- **(iv)** Illogical electrophiles and nucleophiles

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THE LOGIC OF ORGANIC SYNTHESIS

Target Molecule (T.M.):

The molecule to be synthesised, i.e., the molecule whose synthesis is being planned is called the target molecule (TM).

Let we try to synthesize a compound ‘Z’ i.e. ‘Z’ is the target molecule.

Retrosynthetic Analysis or Retrosynthesis:

It is a problem solving technique for transforming the structure of a target molecule (T.M.) to a sequence of progressively simpler structures along a pathway, which ultimately leads to a commercially available starting material (S.M.) for a chemical synthesis.

It is the process of breaking down a target molecule into available starting materials (S.E.) by functional group interchange and disconnection.

We know the structure of ‘Z’ then we have to find out the immediate precursor of the target molecule (Z) from which Z can be obtained by best way the process is continued until we reach a easily available simple starting molecule.

Target molecule (Z) ⟹ first precursors (Y) ⟹ 2nd precursors (Y) ⟹ ⟹ starting material (S.M.) (A)

Let ‘A’ is the starting material (S.M.), now we have to design the synethesis

$$\text{A (SM)} \xrightarrow[\text{reactions}]{\text{By chemical}} \text{B} \longrightarrow \text{C} \longrightarrow \quad \longrightarrow \quad \longrightarrow \text{Y} \longrightarrow \text{Z (TM)}$$

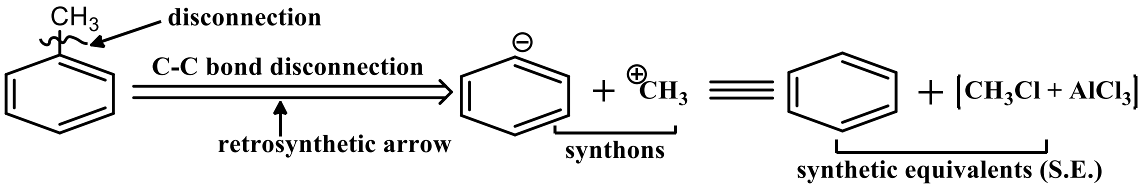
Disconnection:

An analytical operation which breaks a bond and converts a target molecule to a into possible easily available starting materials.

It is the reverse operation to a reaction, which involves an imaginary bond cleavage to break the target molecule into the possible starting material (S.M.)

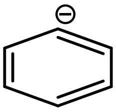
‘⟹’ symbol is used to indicate the reverse of a synthetic reaction (retrosynthetic arrow) and a ‘⌇’ line is drawn through the bond being broken, is used.

Example:



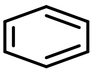
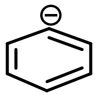
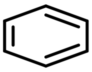
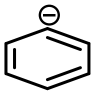
Synthon:

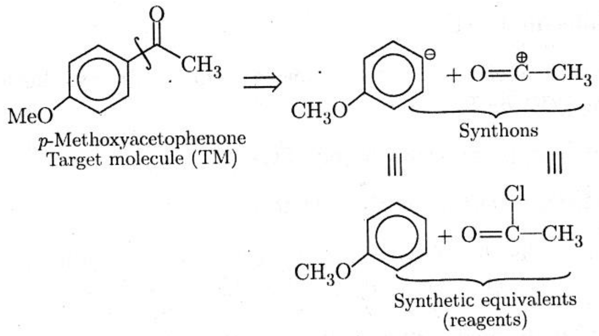
An idealized fragment, usually a cation or an anion resulting from a disconnection is known as synthon. It may or may not be an intermediate in the corresponding reaction.

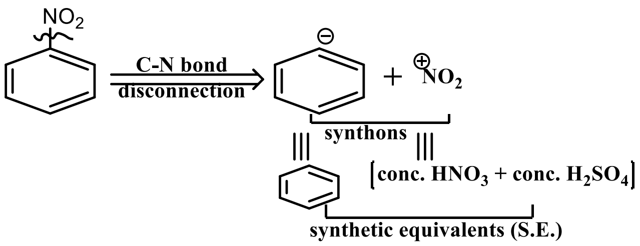
 **and $^{\oplus}CH_3$ are synthons in the above reaction**

Synthetic equivalent (S.E.) or Reagent:

A real chemical compound used in practice as the equivalent of a synthon is called a synthetic equivalent (S.E.) or reagent.

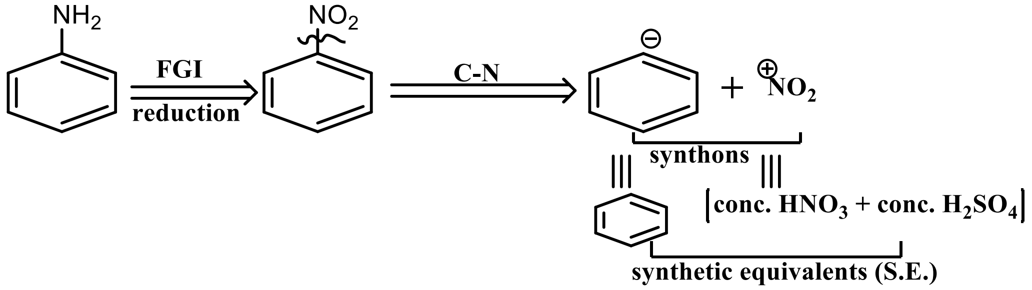
 **is a real chemical compound, act as a source of**  **and CH_3Cl is a real chemical compound, act as a source of $^{\oplus}CH_3$ So,**  **is synthetic equivalent (S.E.) of**  **and CH_3Cl is S.E. of $^{\oplus}CH_3$**

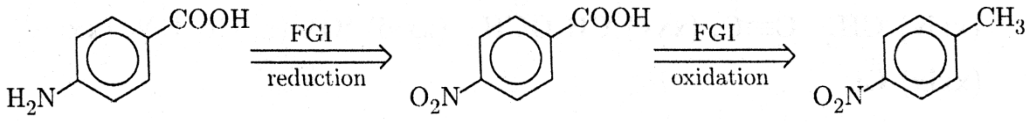




Functional Group Interconversion:

The process of converting one functional group into another by reactions such as substitution addition, elimination, oxidation, or reduction is known as functional group interconversion (FGI) i.e. the replacement of one functional group by another so that disconnection becomes possible.





Functional Group Addition (FGA):

The operation of adding a functional group to facilitate a proper disconnection is known as functional group addition. (FGA)

addition of --CO_2Et group at α C-atom which facilitate the disconnection

Type of Synthons: Donor (**d synthon** and Acceptor (**a synthon**).

A negatively polarised synthon is known as **donor synthon** (denoted by symbol **d**) which may act as a donor and a positively polarised synthon is known as **acceptor synthon** (denoted by symbol **a**) which may act as an acceptor.

We can have an idea about acceptor and donor synthons from the latent polarity of some organic molecules.

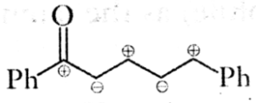
Latent Polarity:

The concept of latent polarity is an imaginary pattern of alternating (+) and (-) charges used to give an idea about the nature of synthons resulting from a disconnection of a target molecule. The polarities are, arranged in such a way that the (+) charge is initially placed on the carbon adjacent to more electronegative oxygen atom. There are two patterns of polarity in the molecule. These are as follows-

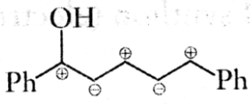
(a) Consonant pattern:

It is a coincident relationship of overlapping latent polarities. In this case, if the latent polarities arising from each of the functional groups are added, they are found to be superimposable. A system containing a 1,3- or 1,5-dioxygen function follows this charge pattern.

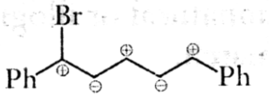
For example, in the following target molecules (1 to 3), if we start either form left hand side C=O or from right hand side C=O/C—OH, we see that the relationship of latent polarities are overlapping, i.e., superimposable. These types of target molecules on disconnection can give synthons of normal polarities and the forward synthesis can be done smoothly with normal synthetic equivalents.



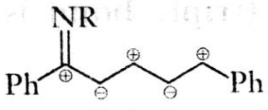
(Ketone)



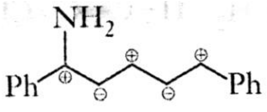
(Alcohol)



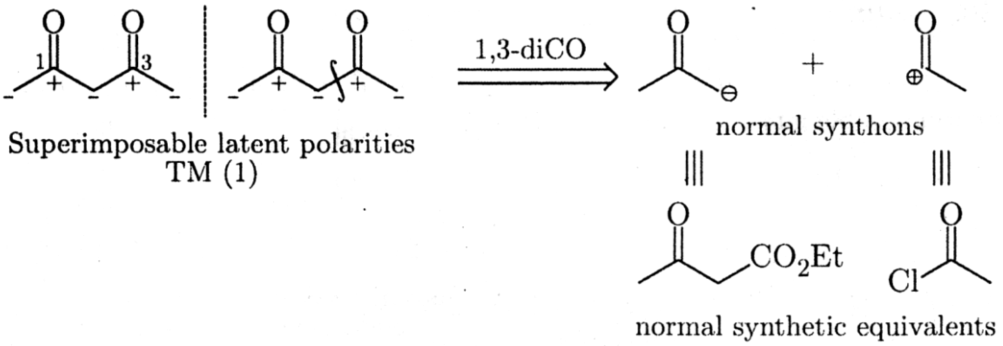
(Bromide)

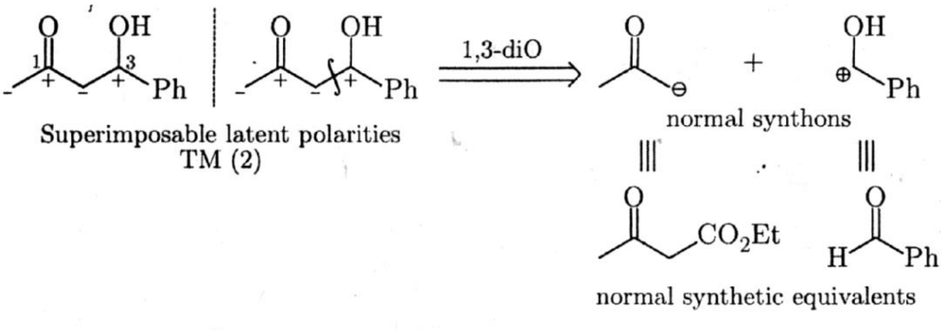


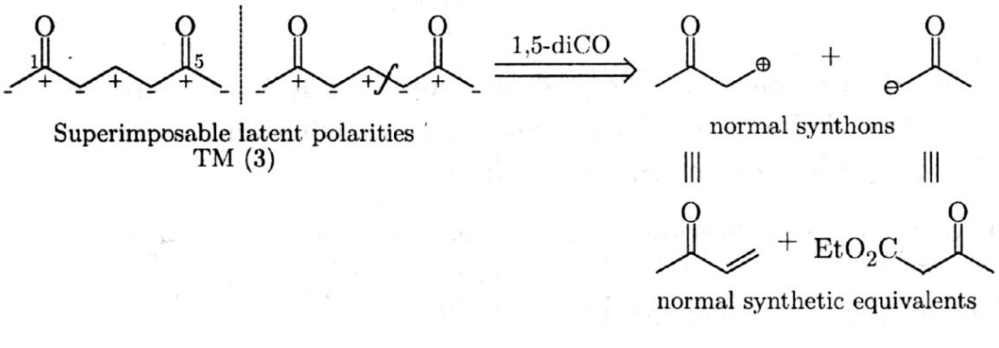
(Imine)



(Amine)



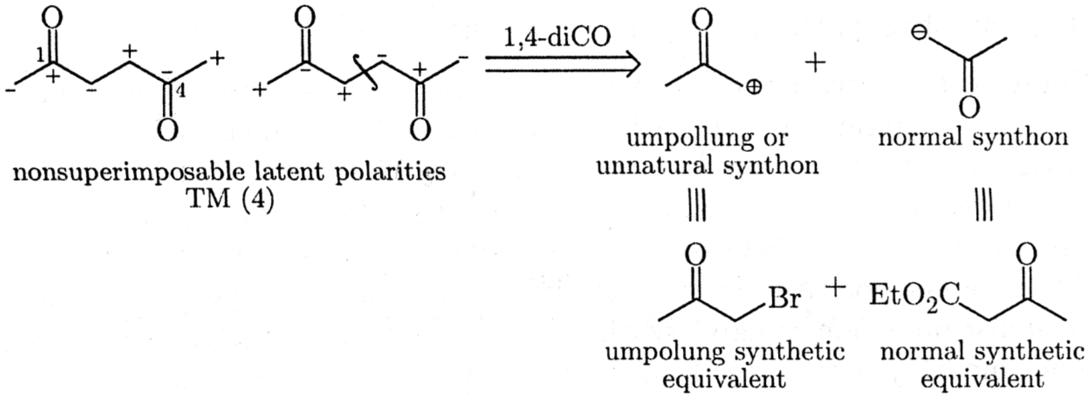




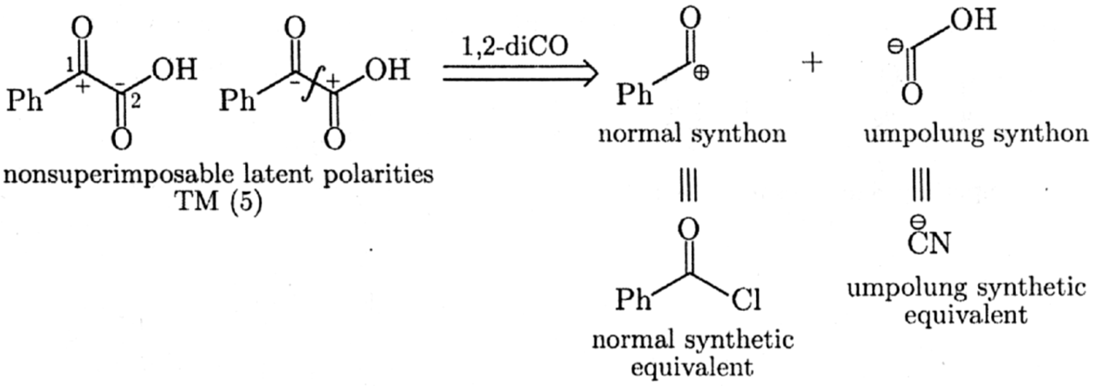
(b) Dissonant pattern:

It is a nonsuperimposable relationship of latent polarities. In this case, if the latent polarities arising from each of the functional groups are added, they are found to be nonsuperimposable. A system containing a 1,2- or 1 ,4-dioxygen function follows this charge pattern. For example, in the following target molecules (4 to 6), if we start either from left hand side C=O or from right hand side C=O/—OH, we see that the latent polarities are not overlapping.

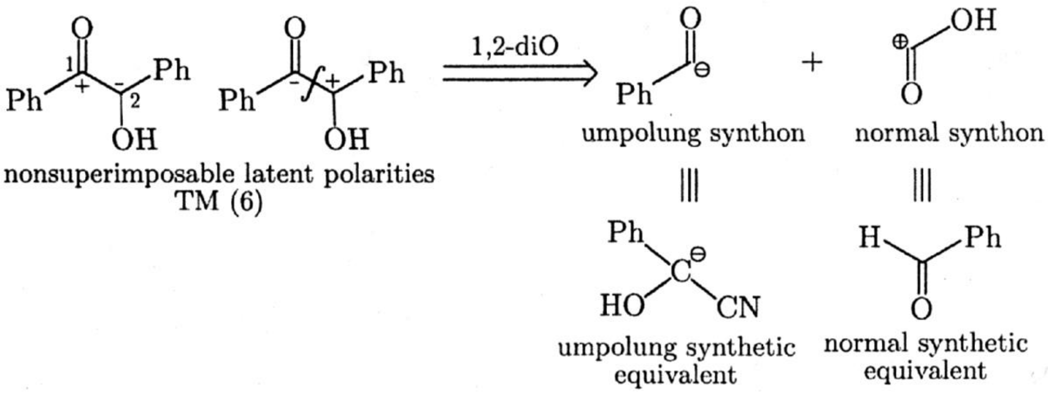
These types of target molecule on disconnection must give synthons of unnatural polarity (umpolung synthons) and the forward synthesis requires umpolung synthetic equivalent or reagents.



nonsuperimposable latent polarities
TM (4)



nonsuperimposable latent polarities
TM (5)



nonsuperimposable latent polarities
TM (6)

On the basis of latent polarity the donor and acceptor synthons may again be divided into two categories; (I natural or logical synthons where natural polarity matches (superimposable) and (II) unnatural or illogical synthons where natural polarity does not match (nonsuperimposable).

Illogical synthons are also known as Umploung (polarity reversal) synthons.

<u>Normal Synthons</u>:

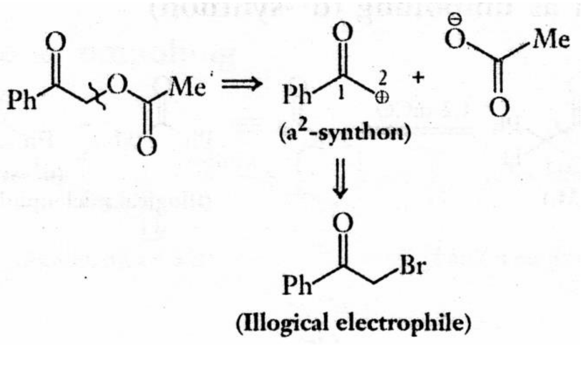
Disconnection of a bond of a target molecule gives ionic synthons either electrophilic or nucleophilic where the normal polarity is preserved is called a natural or normal synthon and the corresponding synthetic equivalent is called a natural or normal synthetic equivalent.

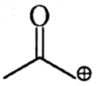
<u>Illogical Electrophile</u>:

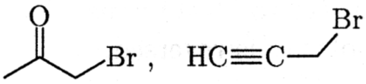
Disconnection of a bond of a target molecule gives positively charged (electrophilic) synthons where the normal polarity is reversed then the synthon is called an unnatural or illogical electrophilic synthon, and the corresponding synthetic equivalent is called illogical electrophilic synthetic equivalent or illogical electrophile.

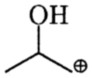
Illogical electrophile can be generated from a^2-synthons.

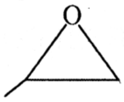
Examples: Generally α-haloketones, epoxides and propargyl halides are example of illogical electrophiles




illogical synthon
(electrophilic)


Bromoacetone, Propargyl bromide
illogical synthetic equivalent (electrophilic)
or illogical electrophiles


illogical synthon
(electrophilic)


illogical synthetic
equivalent (electrophilic)
or illogical electrophile

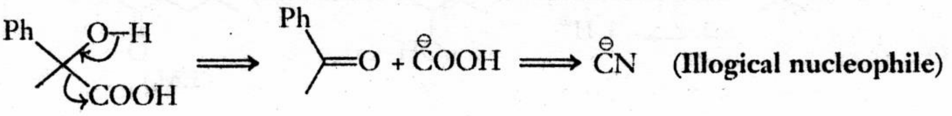
The α–carbon atom of a carbonyl compound is normally nucleophilic. The α–carbon atom in bromoacetone is electrophilic. The polarity is, therefore, reversed. So, bromoacetone is an illogical electrophile.

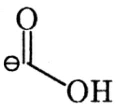
Illogical Nucleophile:

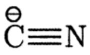
Disconnection of a bond of a target molecule gives negatively charged (nucleophilic) synthons where the normal polarity is reversed then the synthon is called an unnatural or illogical nucleophilic synthos, and the corresponding synthetic equivalent is called illogical nucleophilic synthetic equivalent or illogical nucleophile.

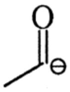
The illogical nucleophiles are generated from d^1-synthons.

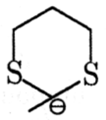
Examples: ⁻CN, dithianes, nitroalkanes, acetylene and monosubstituted alkynes are examples of illogical nucleophiles.




illogical synthon
(nucleophilic)

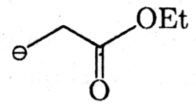

illogical synthetic
equivalent (nucleophilic)
or illogical nucleophile


illogical synthon
(nucleophilic)

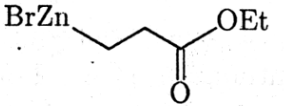

illogical synthetic
equivalent (nucleophilic)
or illogical nucleophile

The carbonyl carbon is normally electrophilic. But in ⁻CN, it is nucleophilic, i.e., the polarity is reversed.

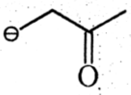
The carbonyl carbon is normally electrophilic. However, when a carbonyl compound is converted to a cyclic thioacetal (a dithiane derivative) and the thioacetal is treated with base, the same carbonyl carbon becomes nucleophilic, i.e., the polarity is reversed.



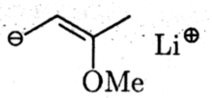
illogical synthon (nucleophilic)



illogical synthetic equivalent (nucleophilic) or illogical nucleophile



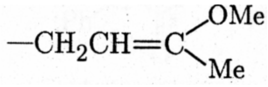
illogical synthon (nucleophilic)



illogical synthetic equivalent (nucleophilic) or illogical nucleophile

The β–carbon atom with respect to C=O is usually electrophilic. In Reformatsky, reagent it is nucleophilic, i.e , the polarity is reversed

The carbon atom β– to C=O is usually electrophilic (as in an α,β-unsaturated carbonyl compound). The lithium salt may be regarded as an illogical nucleophile because the

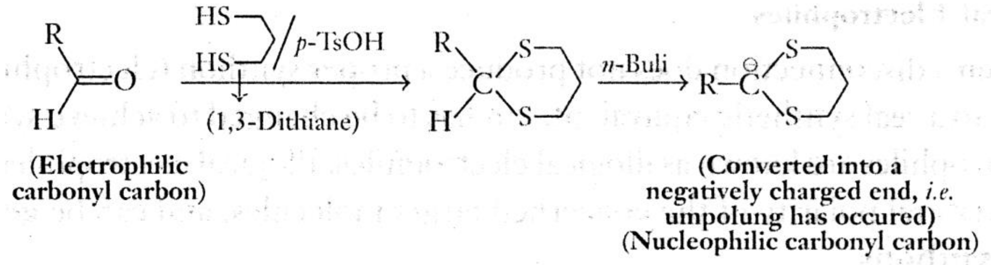


$-CH_2CH{=}C(OMe)(Me)$ moiety is the FGI of $–CH_2CH_2COCH_3$ group

Umpolung:

The reversal of polarity is known as umpolung.

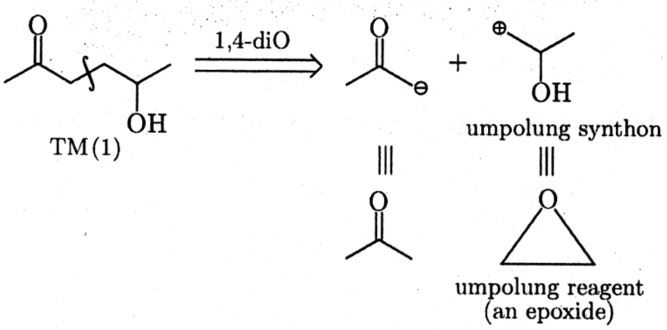
Generally the carbonyl carbon is positively polarised, i.e., electrophilic, hut if it is converted to a negatively charged atom, i.e. a nucleophilic centre, then the phenomenon is known as umpolung.

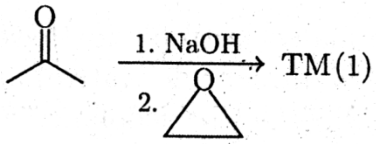


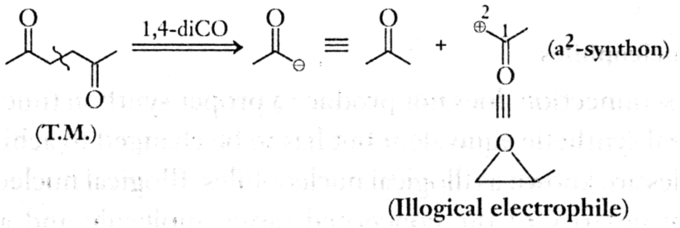
Syntheses involving umpolung synthetic equivalents or reagents are called umpolung synthesis.

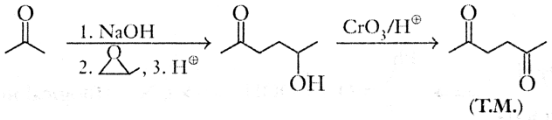
1. Use of epoxide as umpolung (a^2-synthon)

Retrosynthetic analysis: **Synthesis:**



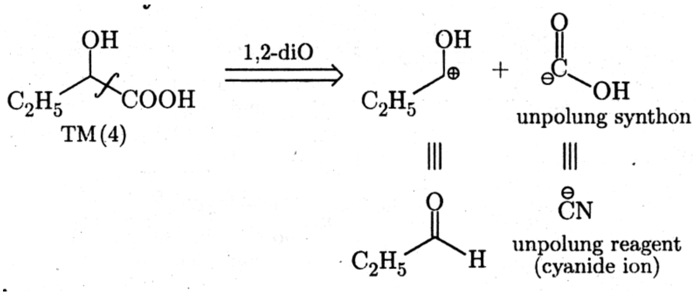




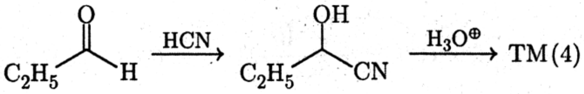


2. Use of ⁻CN ion as umpolung (d¹ -synthon)

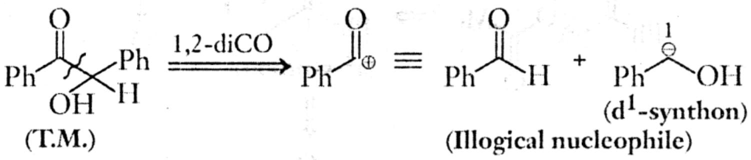
Retrosynthetic analysis:



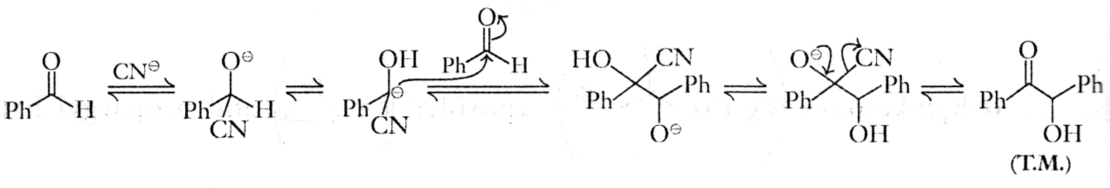
Synthesis:



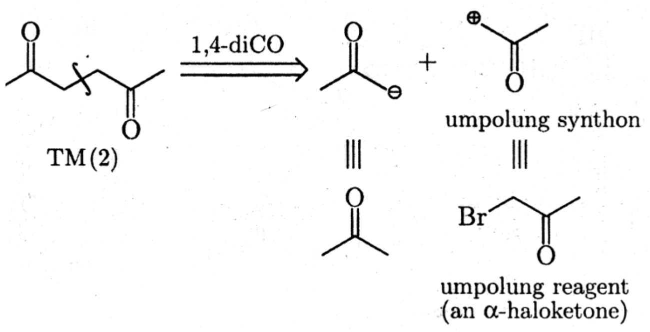
Retrosynthetic analysis:

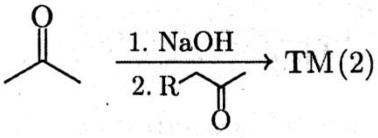


Synthesis: (Benzoin condensation)



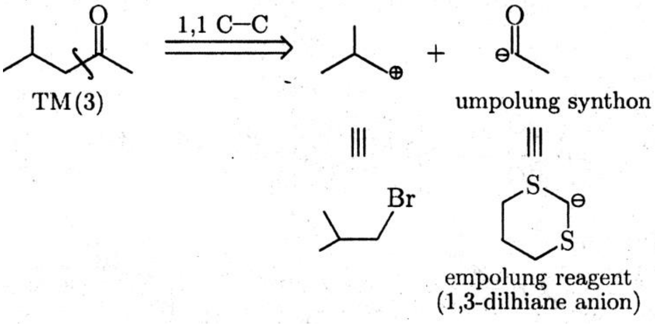
3. Use of α-haloketones or esters as umploung (a²-synthon)



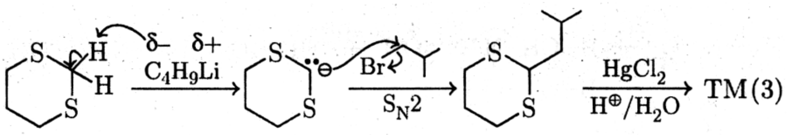


4. Use of dithiane as umpolung

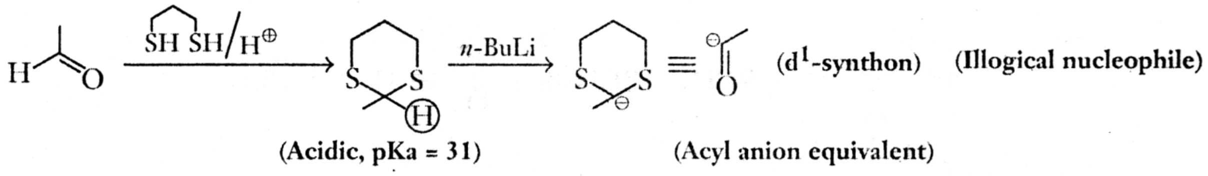
Retrosynthetic analysis:



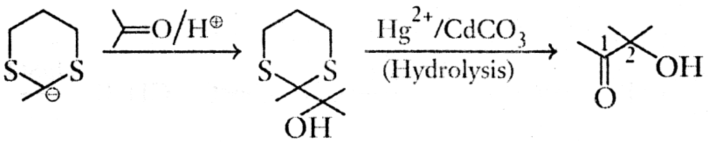
Synthesis:



Retrosynthetic analysis:

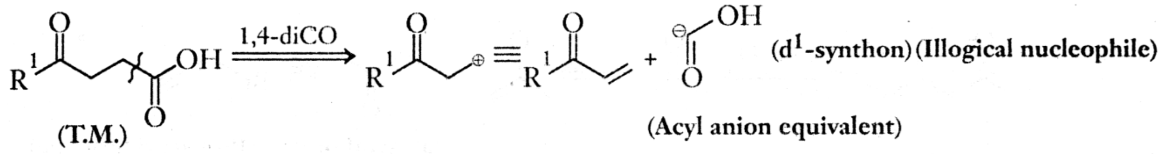


Synthesis:

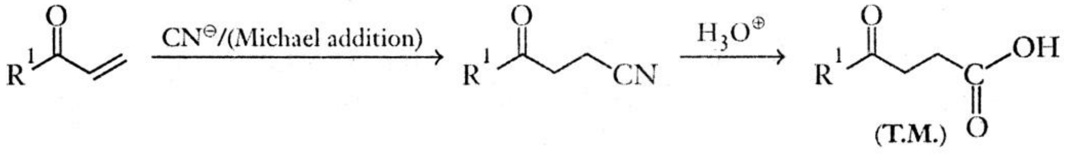


5. Cyanide and nitroalkane anions as umpolung which are also good acyl anion equivalents. (d^1 -synthon)

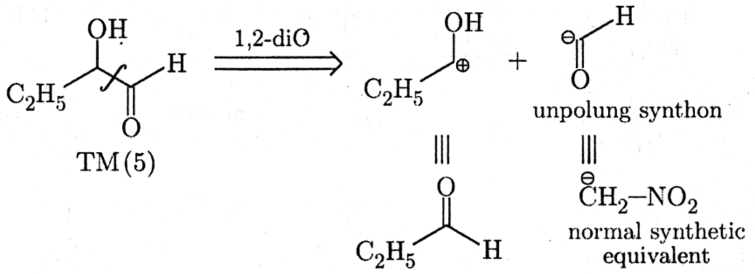
Retrosynthetic analysis:



Synthesis:



Retrosynthetic analysis:



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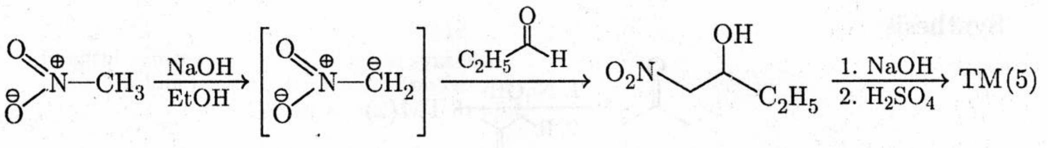
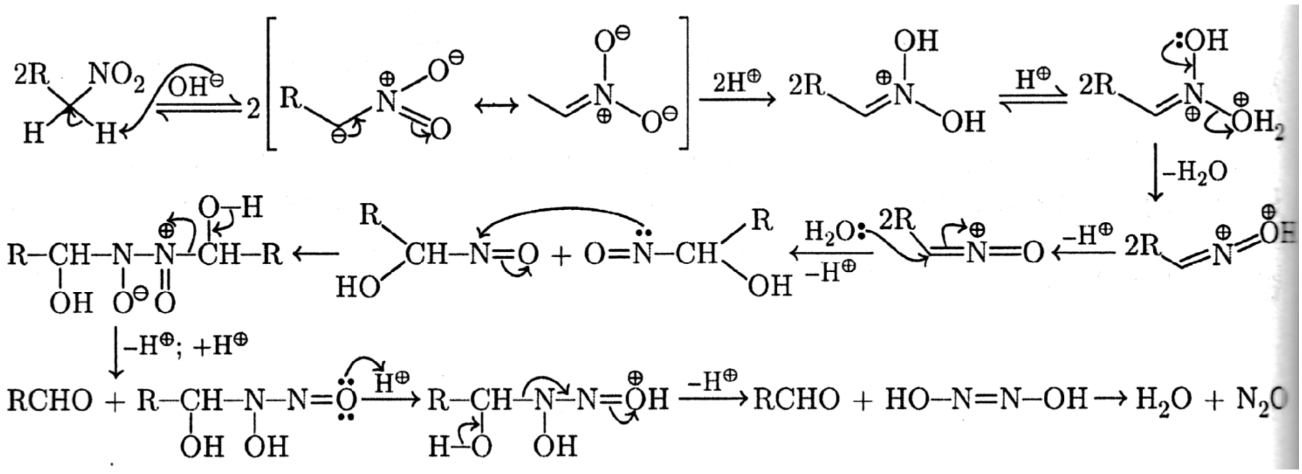


The conversion of primary or secondary aliphatic nitro compounds into the corresponding carbonyl compounds by means of hydrolysis of their conjugate bases (nitronate salt) with sulphuric acid is called the **Nef reaction**. The mechanism of the reaction is as follows—



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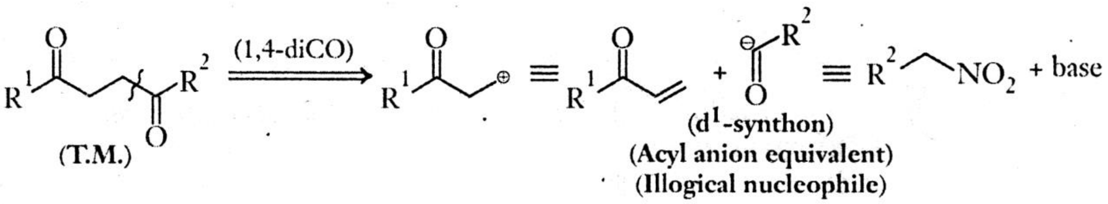

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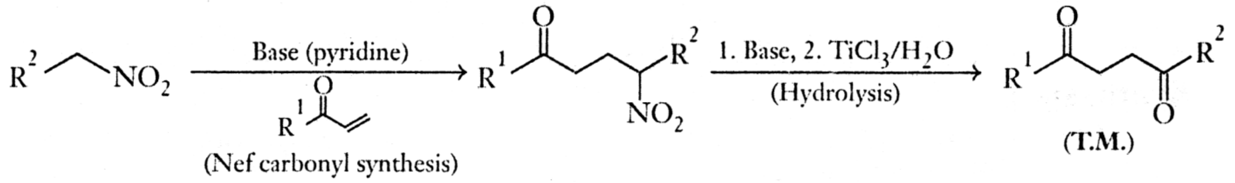
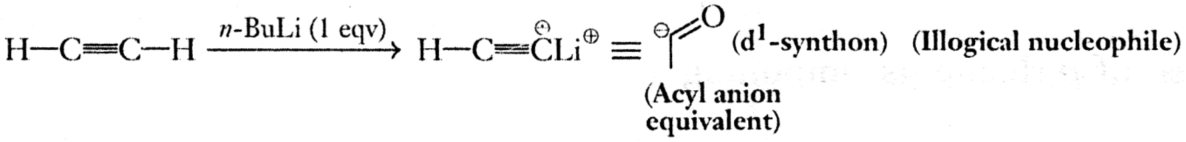
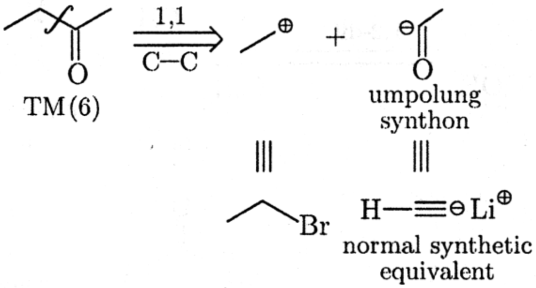


6. Alkynes as umpolung and a good acyl anion equivalent (d^1—synthon)



Analysis:



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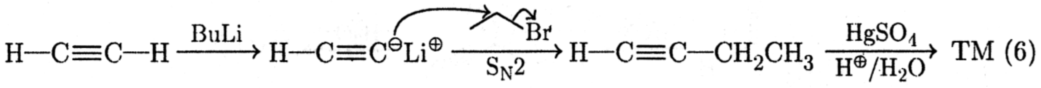
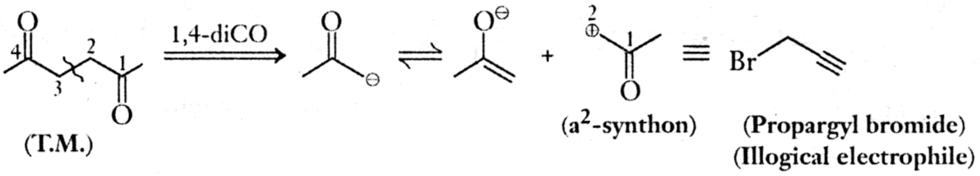


7. Propargyl halide as umpolung:

Retrosynthetic analysis:



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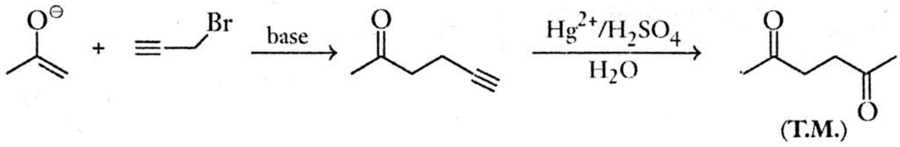

base
Hg^{2+}/H_2SO_4
H_2O
(T.M.)