CHEM – 478

Organic synthesis

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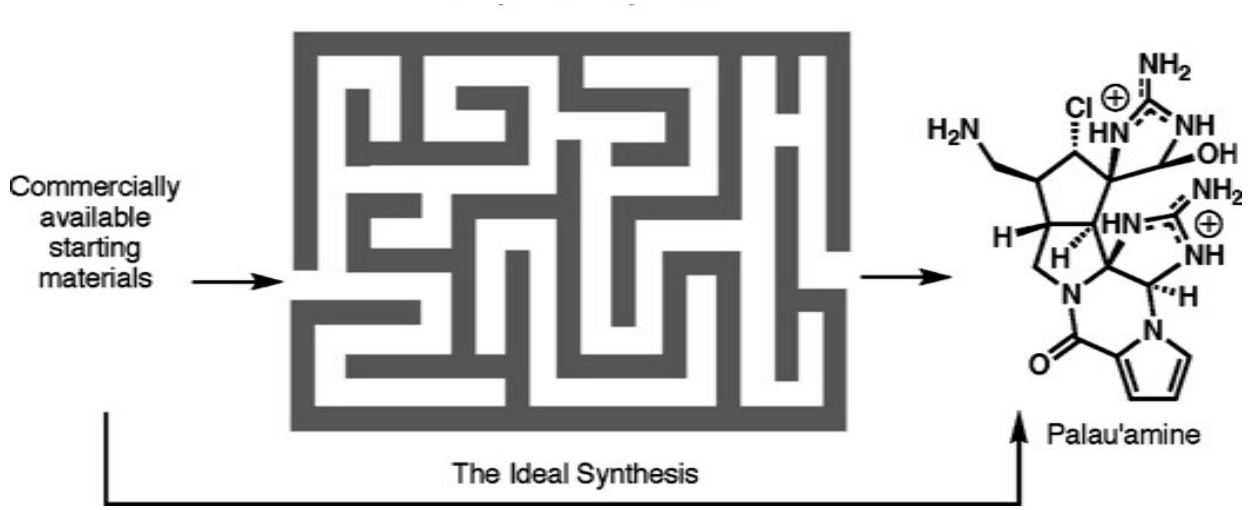
RETROSYNTHETIC ANALYSIS



The ultimate goal of Organic Synthesis is to assemble an organic compound (target) from readily available starting materials and reagents in the most efficient way.

This process usually begins with the design of a synthetic plan (Strategy)

Ideal Synthesis

Economically acceptable

Cost effective: Less expensive starting materials

Environmentally acceptable

Green route: avoid wastes side products and toxic intermediates

Safe

Avoid risky and hazardous procedures

Robust

Easily scale-up and reproduceable

Highly efficient

Simple, high yield, a few steps

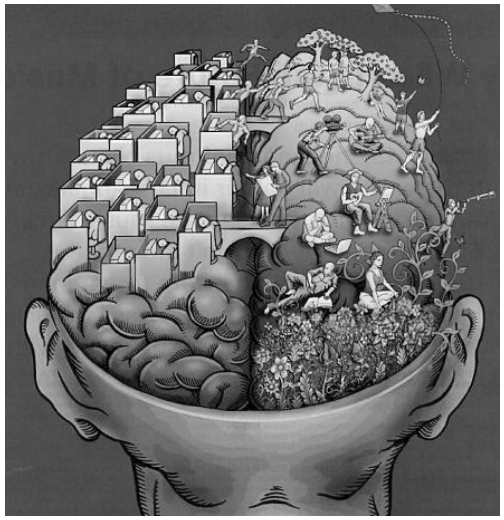
Requirements for Ideal Synthesis

1. ***Knowledge of Reactivity (Structure-Mechanism)*** ***Tactics***

2. ***Design ability (Retrosynthetic Analysis)*** ***Strategy***

LEFT BRAIN

Logic
Analysis
Organization
Knowledge /Facts
Detail
Maths & Science



RIGHT BRAIN

Intuition
Emotion
Spirituality
Belief
Big picture
Art / Music

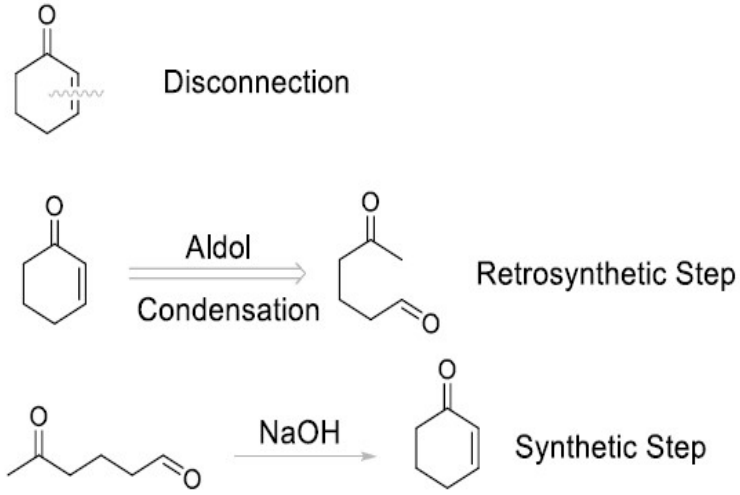
Synthesis is logical as well as artistic activity at the same time. It involves freedom, imagination, creativity, courage, persistence, knowledge and skills

RETROSYNTHETIC ANALYSIS

Retrosynthetic analysis is a problem solving technique for transforming the structure of a synthetic target molecule (TM) to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials for a chemical synthesis.

- **Reverse of Synthesis is the process of breaking down the TM into available starting materials by FGI and disconnection**

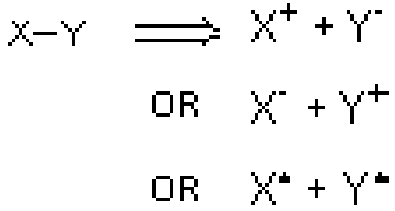
- **Disconnection is reverse operation to a reaction: An imaginary cleavage of a bond to break the molecule into starting materials (≀)**



TM ⟹ 1st Precursor ⟹ 2nd Precursor ⟹ Starting compounds - readily available

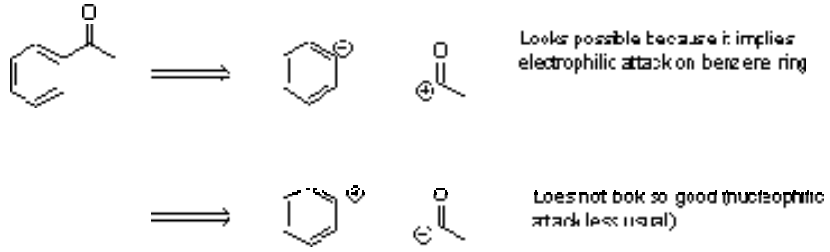
RETROSYNTHETIC ANALYSIS

Disconnection



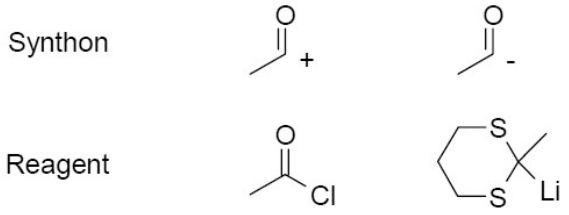
Synthon

An idealised fragment **resulting from disconnection*, usually cation or anion***



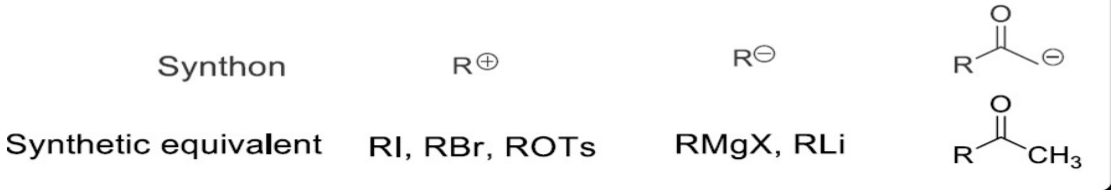
Reagent

compound used in practice for a synthon.



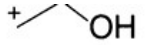
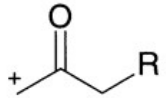
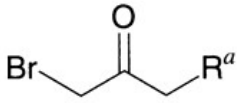
Synthetic Equivalent

Actual substrates used for the forward synthesis



RETROSYNTHETIC ANALYSIS

Acceptor synthon : carbocation (electrophilic)

Common Acceptor Synthon	Synthetic equivalents
R^+ (alkyl cation = carbenium ion)	RCl, RBr, RI, ROTs
Ar^+ (aryl cation)	$ArN_2^+ X^-$
$RC^+{=}O$ (acylium ion)	$RC(=O)-X$ (X = Cl, NR_2', OR′)
$^+CH_2CH_2C(=O)-R$	$CH_2{=}CHC(=O)-R$ (R = alkyl, OR′)
$^+CH_2OH$ (oxocarbenium ion)	HCHO
	
	

RETROSYNTHETIC ANALYSIS

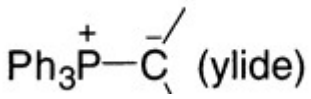
Donor synthon :

Common Donar Synthon

R^- (alkyl, aryl anion)

^-CN (cyanide)

$RC{\equiv}C^-$ (acetylide)

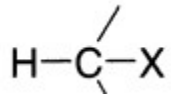


enolate

Carbanion (nucleophilic)

Synthetic equivalents

$RMgX$, RLi, R_2CuLi	$R{-}X$
$NaC{\equiv}N$	HCN
$RC{\equiv}CMgX$, $RC{\equiv}CLi$	$RC{\equiv}CH$



carbonyls

RETROSYNTHETIC ANALYSIS

FGI-Functional Group Interconversion

Functional group interconversion (FGI) describes a process of converting one functional group to another: e.g. an alcohol to an aldehyde, alkyne to alkene etc.

It is the process of writing one functional group for another to help synthetic planning and to help disconnection. Note, there must be a good reaction in the reverse (forward!) direction.