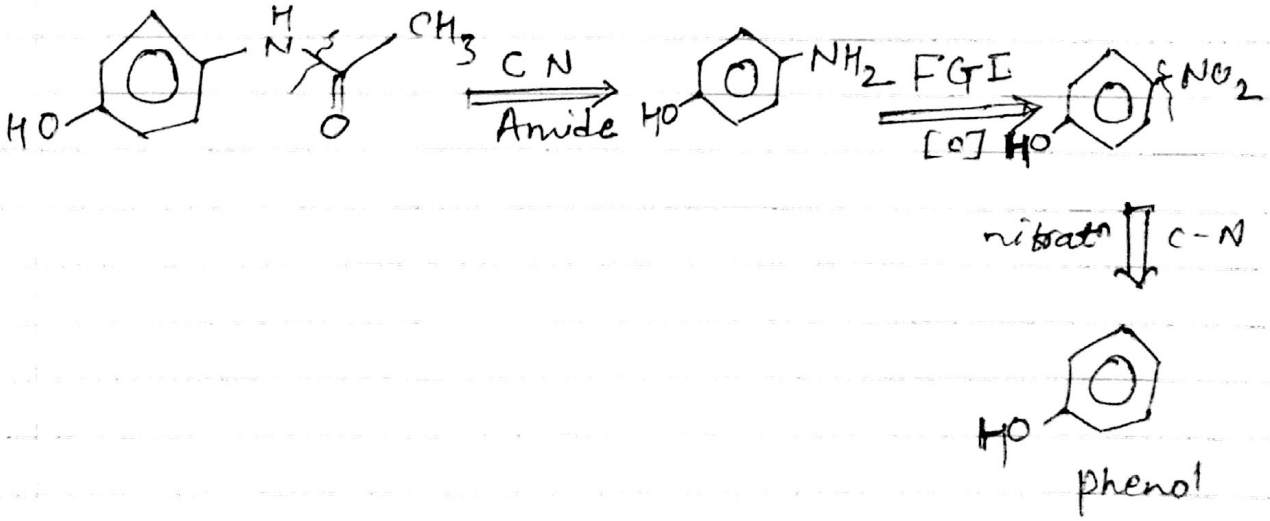
Paracetamol (Acetaminophen):

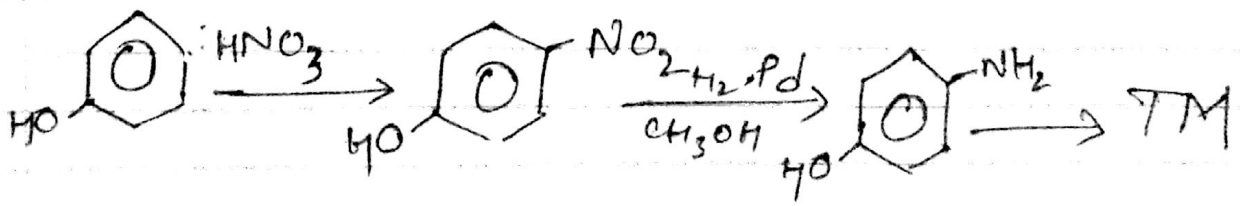
The commonly used analgesic paracetamol is simple amide and should be available by acetylation of p-aminophenol paracetamol.

In paracetamol the disconnection of bond adjacent to heteroatom (N) is occuring which produces p-amino phenol which undergoes FGI [O], the NH_2 is converted int NO_2 to give p-nitro phenol. This p-nitrophenol again undergoes disconnection next to the heteroatom to give phenol.

Analysis:



Synthesis:

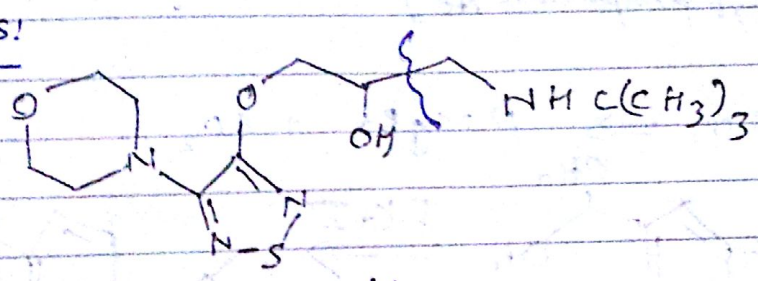


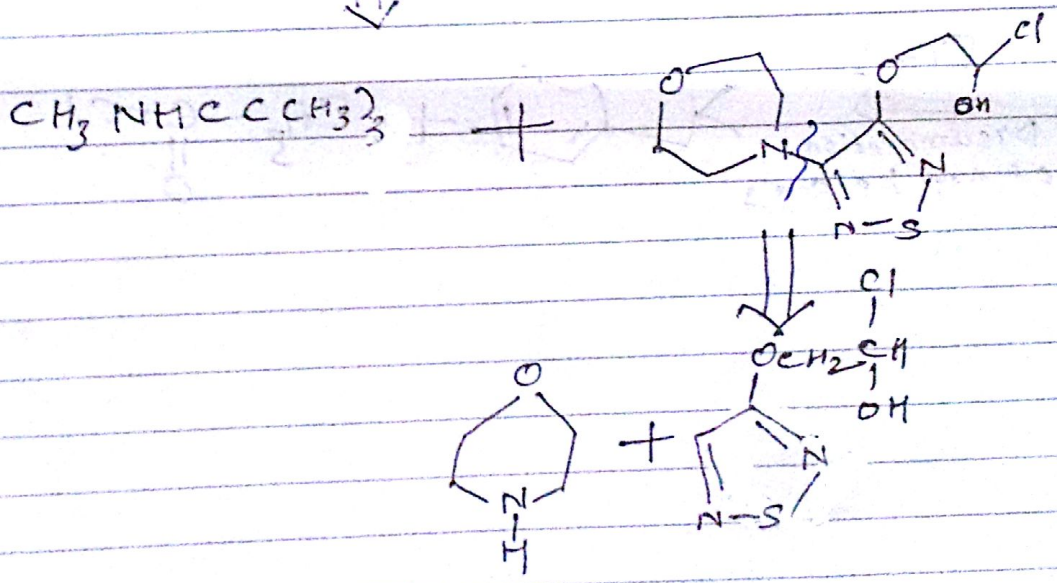
Atenolol:

It is used as β-blocker in the control of hypertension. The structure is analogous to propanolol.

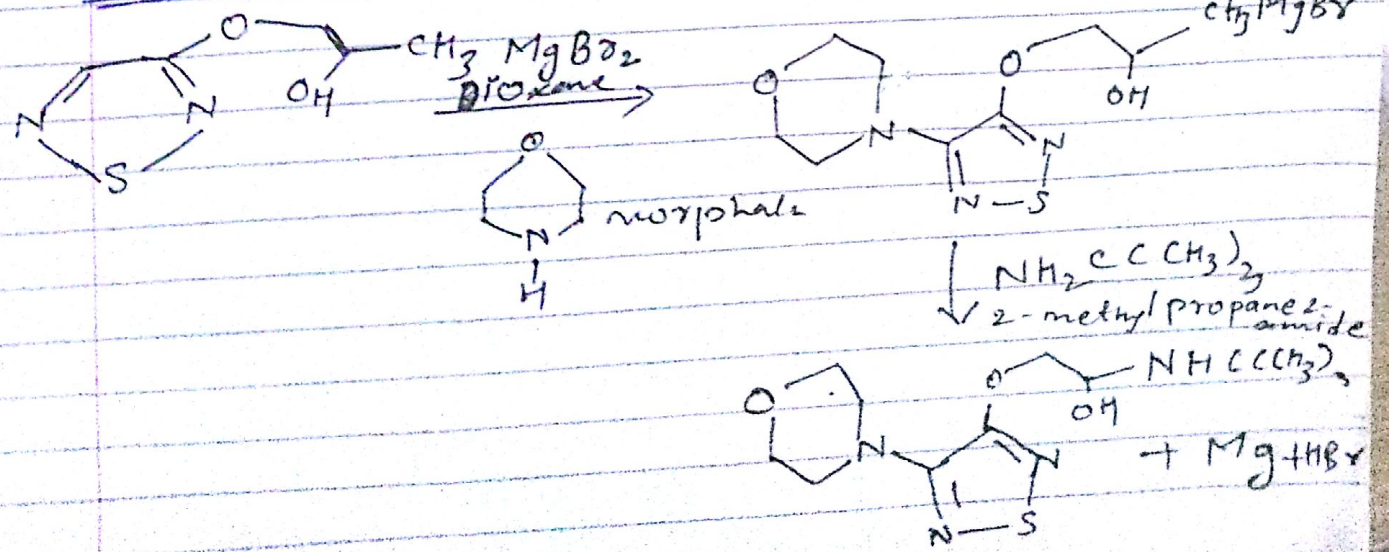
The disconnection of bond occurs next to the heteroatom. whatever the synthons are getting.

Analysis:



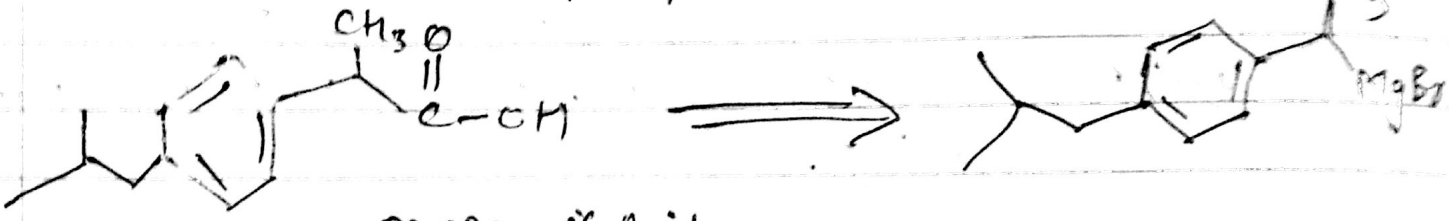


Synthesis:



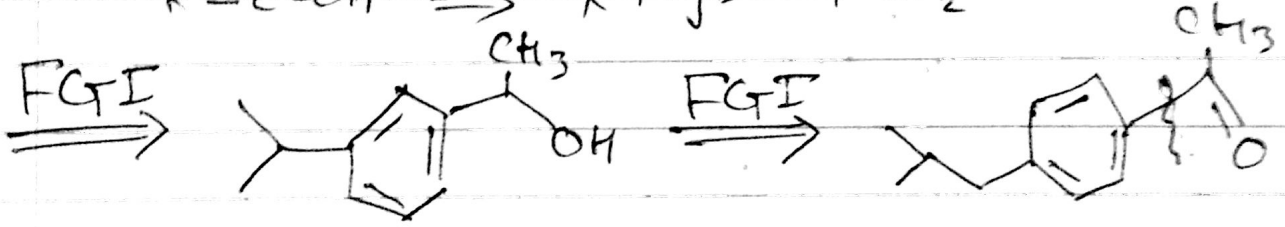
Ibuprofen (Propanoic Acid derivatives)
(anti-inflammatory / Analgesic)

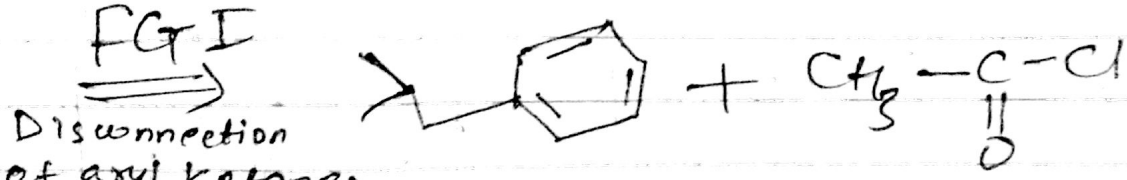
Iso butyl phenyl propanoic Acid



Isobutyl phenyl propanoic Acid

$$R-\overset{O}{\overset{\|}{C}}-OH \Longrightarrow RMgBr + CO_2$$



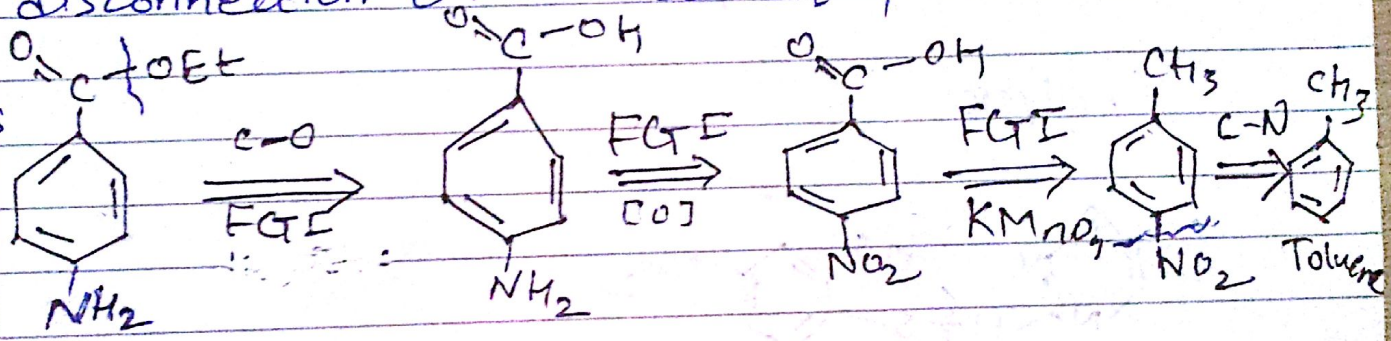


Disconnection of aryl ketones.

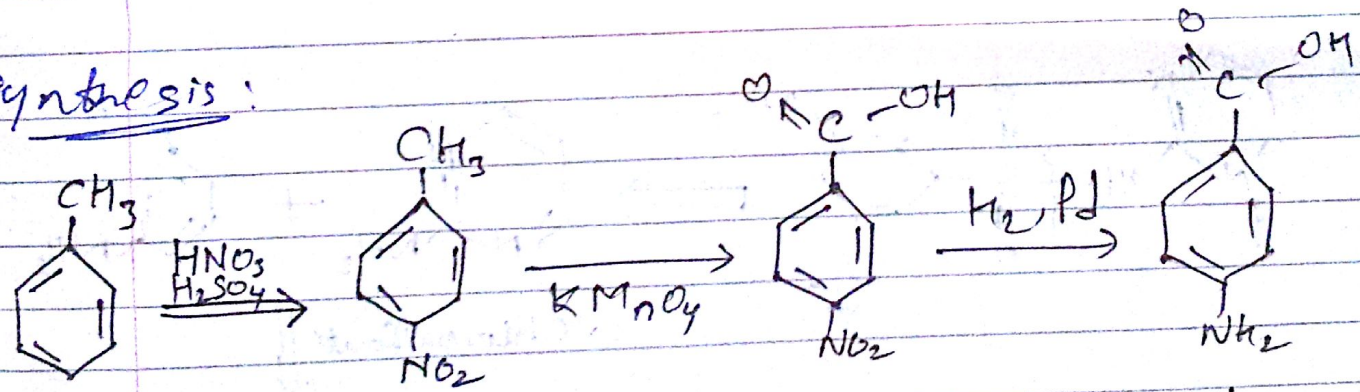
Benzocaine:

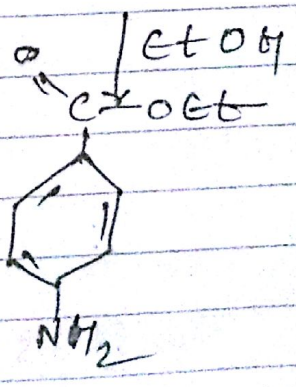
In Benzocaine the disconnection b/w C & O is carried out to produce Acid from ester, that gives compound p-amino benzoic acid. p-Amino benzoic Acid undergoes FGI to produce p-Nitro benzoic acid which on FGI is converted to p-nitro toluene. p-Nitro toluene undergoes disconnection of C–N bond to produce toluene.

Analysis



Synthesis:

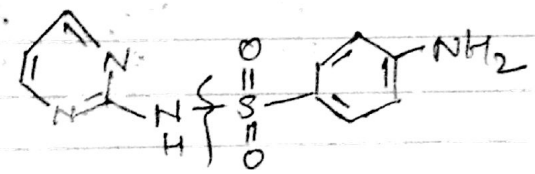


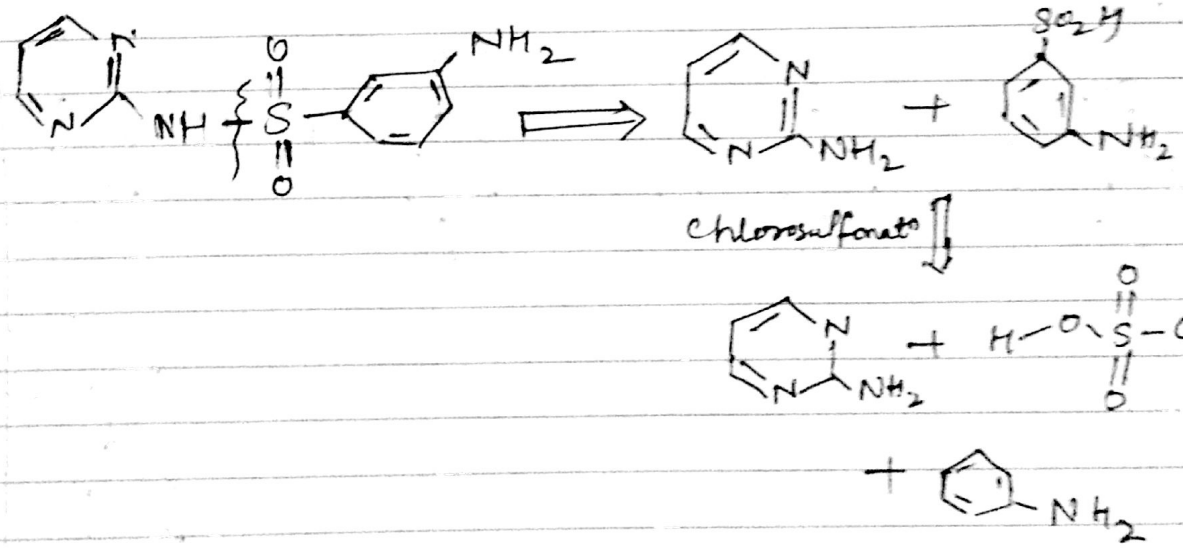


Sulfadiazines:

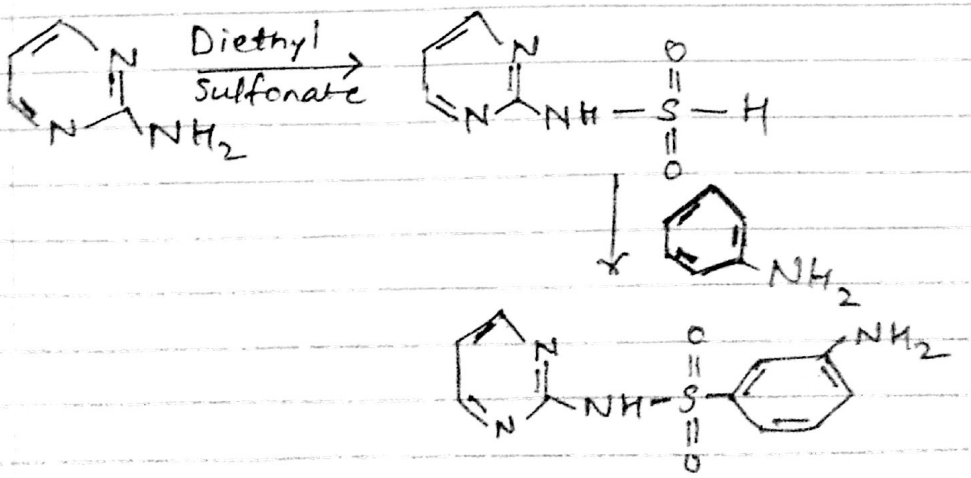
These are of sulphonamide antibiotics. This compound undergoes disconnection by applying disconnection to adjacent to hetero atom. The synthon approach again undergoes FGI to eliminate SO_2Cl which converts Amino group into its derivative to produce starting material i.e Aniline.

Analysis:





Synthesis:



SYNTHON APPROACH

-> If chemistry is the science of matter and of its transformation
-> synthetic chemistry is the science of constructing molecules from atom and/or simpler molecules.
-> chemical synthesis :- The preparation of a desired organic compound from readily available starting materials can be defined as organic synthesis.

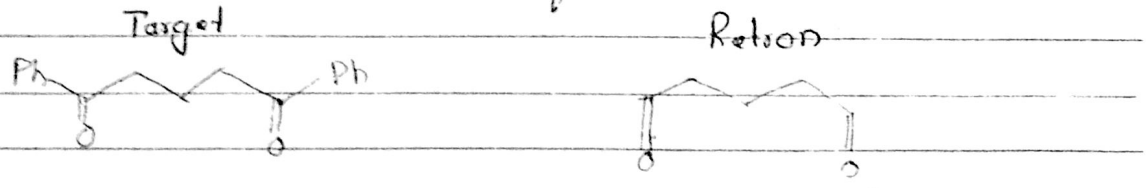
Retrosynthetic analysis :-
The logical process of analyzing the structure of a target molecule to transform the target to a sequence of progressively simpler structures along a pathway which finally will lead to simple or commercially available starting materials.

Transform :- The reverse of a synthetic reaction, to a target structure.

Retron :- The transform is applied on a structural subunit contained into the target compound

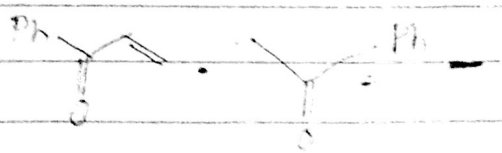
$$A \Longrightarrow B.$$

B is a precursor of A. The arrow means "can be made form"



Transform
Michael

Precursors (s)



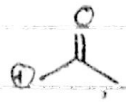
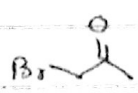
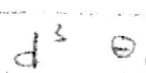
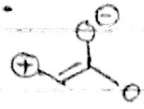
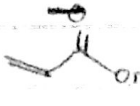
Disconnection :- Cleavage of a bond to break the target into two possible starting materials.
Synthons :- An idealized (often charged) molecular fragments
d$_n$ synthons :- Functionalized nucleophile
D = Donor n = distance between the FG & reactive center

→ Synthon :- Functionalized electrophile & a - Acceptor

Reagent or synthetic equivalent :-
chemical compound used in practice for a synthon.

It is tree of intermediate
↓ chemical structures
Nodes
↓ Pathways from bottom to top
Synthetic Routes to Target
↓
such tree is called
EXTGT
(As grow out from target).

→ control of RS is very important to avoid explosive branching

Synthon "d"				Synthon "a"			
Type	Example	Reacting material	FG	Type	Example	Reacting material	FG
d^0	$MeS^{\ominus}$	MeSH	>C-S-	a^0	$^{\oplus}PMe_2$	$ClPMe_2$	Me_2P-
d^1	$^{\ominus}C{\equiv}N$	KC≡N	-C≡N	a^1			-CO-
d^2	$^{\ominus}CH_2CHO$	CH_3CHO	-CHO	a^2			-CO-
d^3		HC≡C-COOMe	$-CO_2Me$	a^3			-COOMe
Alkyl-d	$Me^{\ominus}$	MeLi		Alkyl a	$Me^{\oplus}$	MeI	

Functional group interconversion :-
changing of a group in the target molecul into a different one to see if it gives an accessible intermediate.

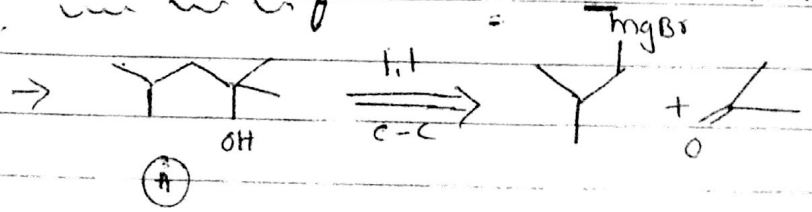
Strategies for Disconnection approach :-
→ There are two types of useful general strategies.
(1) Transform-based strategies :- Structure analysis
Based on the application of powerfully simplifying transform
(2) Structure-based strategies :-
Based on the recognition of possible starting materials or key intermediates for synthesis

→ General strategies (Synthesis)
(1) Functional group based strategies :-
Identify functional groups as key structure subunits.

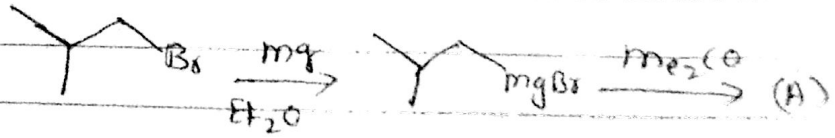
(2) Topological Strategies :- Based on identification of one or more individual bond disconnection or correlated bond-pair disconnection as strategic.

(3) Stereochemical-based strategies
Remove stereocenters and stereorelationship under control.

Disconnection of alcohol :- Analysis :-

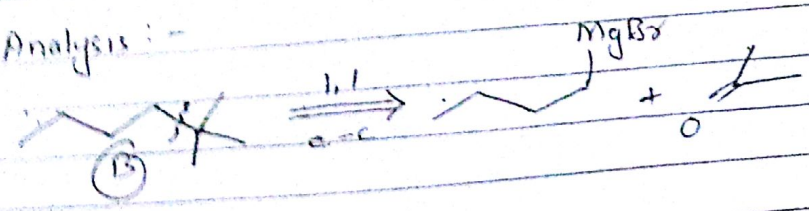


Synthesis :-

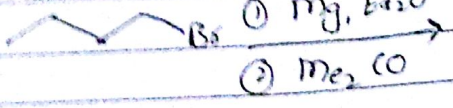


alcohol, Alkylhalide ether, olefins esters COOH, Aryl ketone Heterocyclic comp

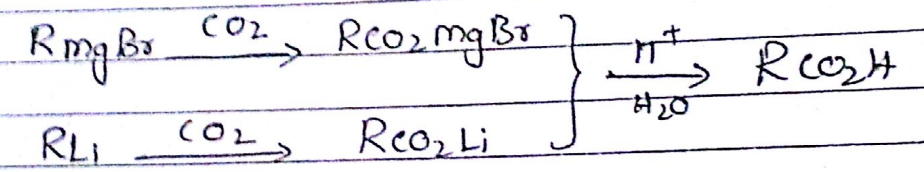
Analysis :-

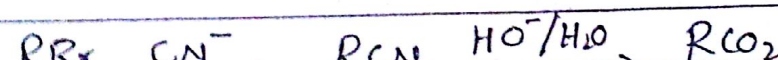


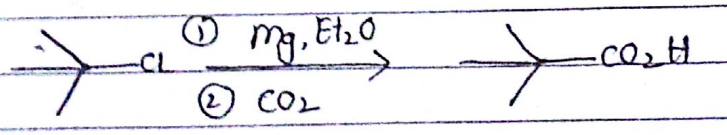
Synthesis



Carboxylic acid :- Direct disconnection is possible in this process eg of oxidation. Here the Grignard methods works well



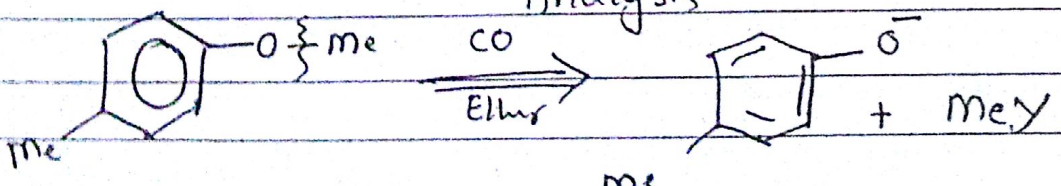




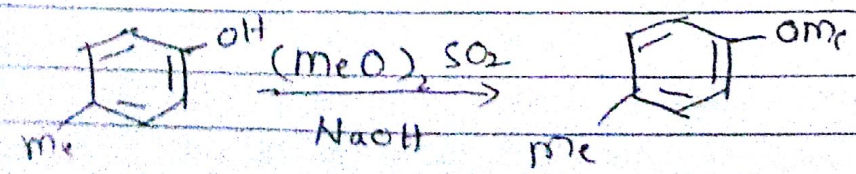
Disconnection with ether :-

if one side of the target molecule is reactive, then disconnect the reactive with unreative

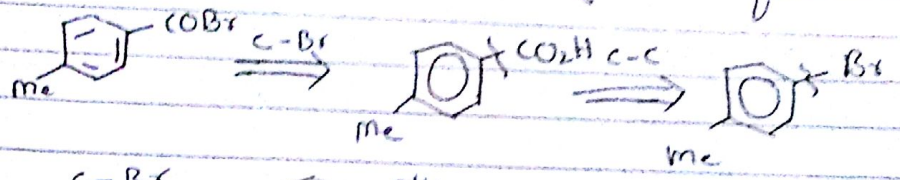
Analysis

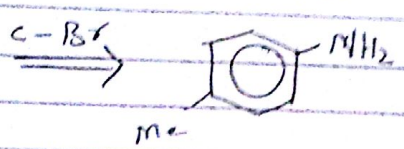


= synthesis

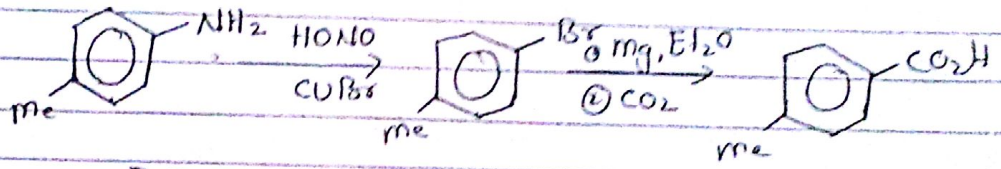


Alkyl halide:- It leads to synthesis of Amines.



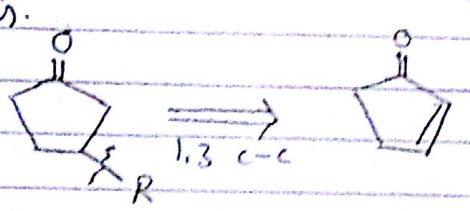


Synthesis :-

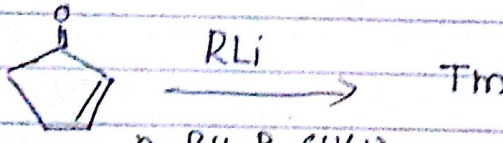


$\xrightarrow{PBr_3}$ Tm.

Carbonyl compound synthesis Michael addition:- when the compound used may having aldehydes or ketone FG. 1,3 addition.



Analysis



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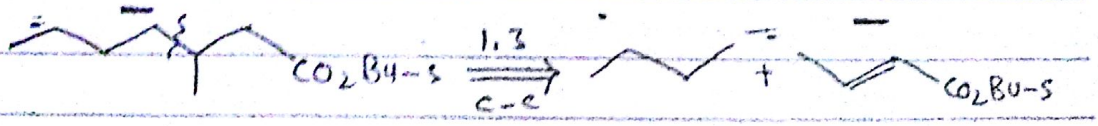
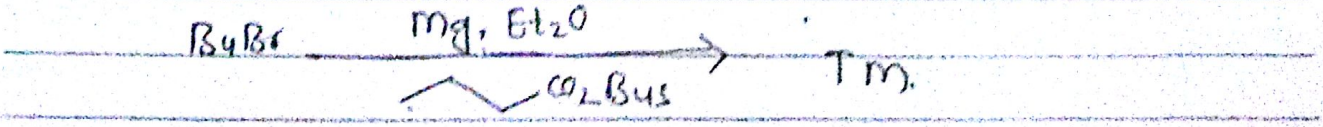
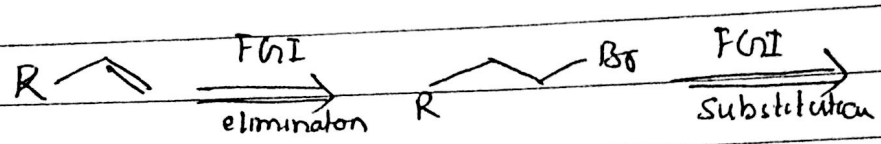


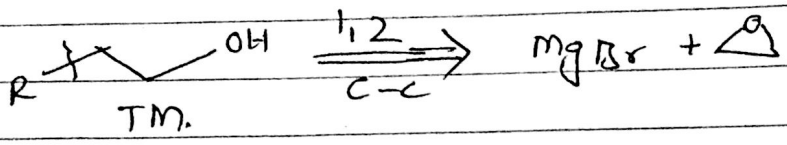
Synthesis



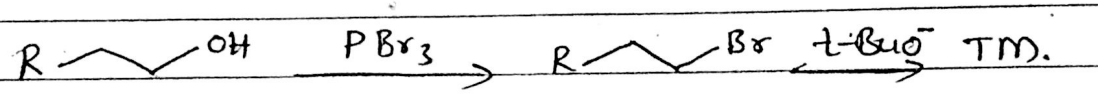
Olefines :-
Olefine can be made by dehydration of alcohols usually under acidic condition.

Analysis



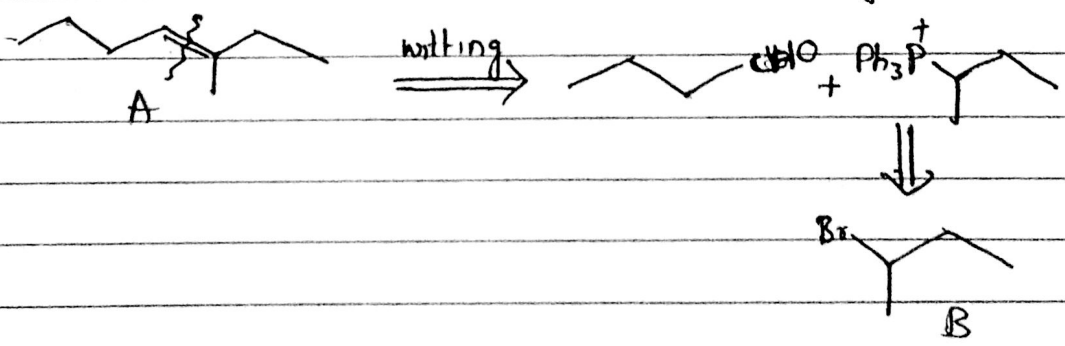


synthesis

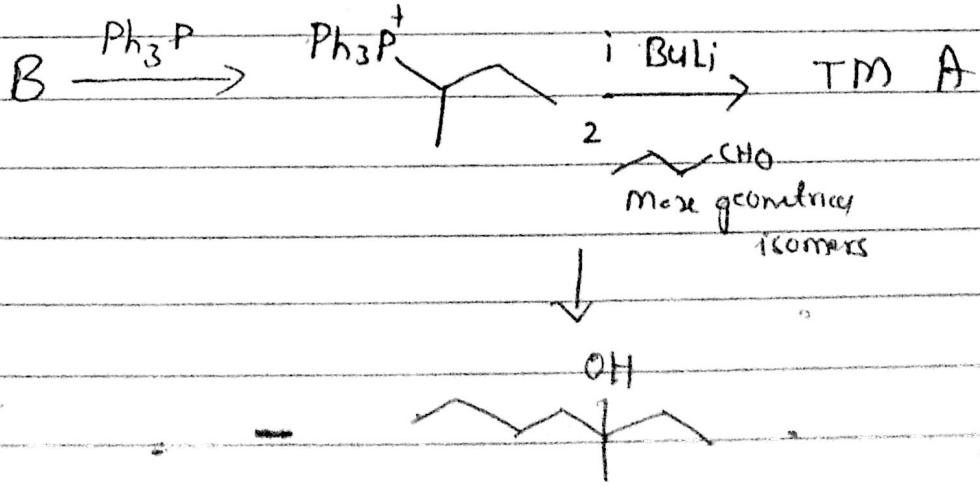


- : Wittig reaction :-

Analysis

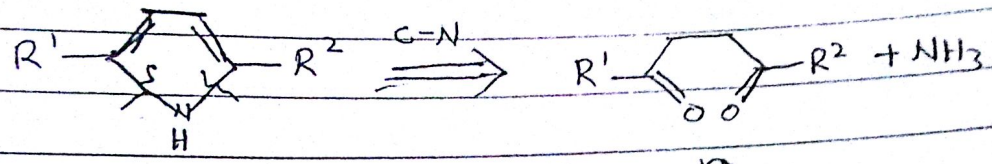


Synthesis.



Heterocyclic ring Disconnection

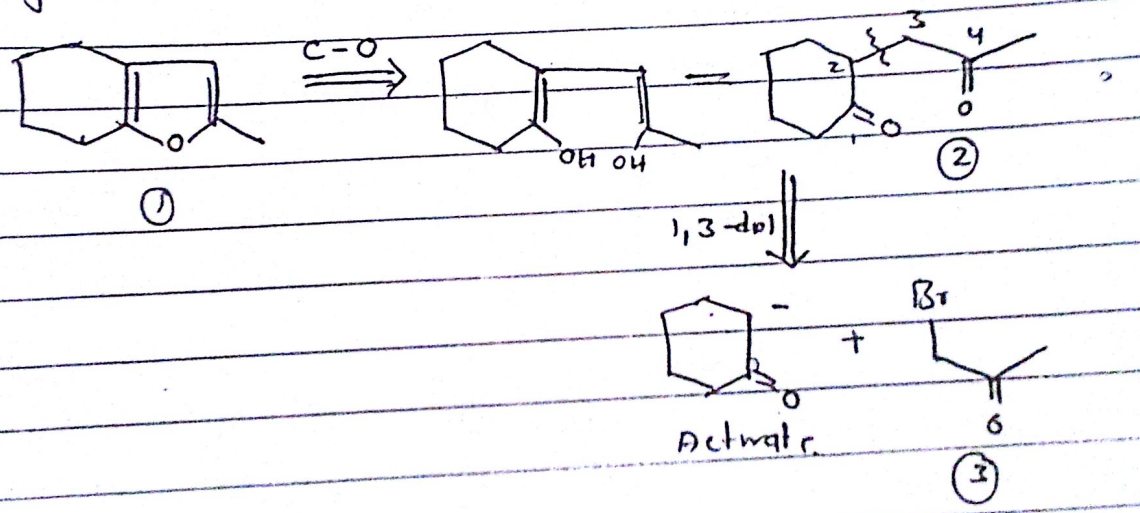
Analysis



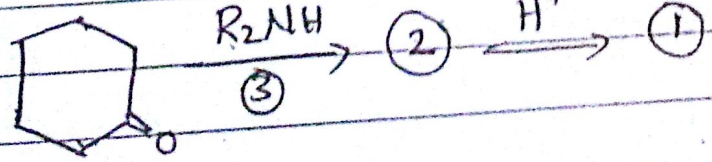
A (B)

Disconnection gives simple starting materials

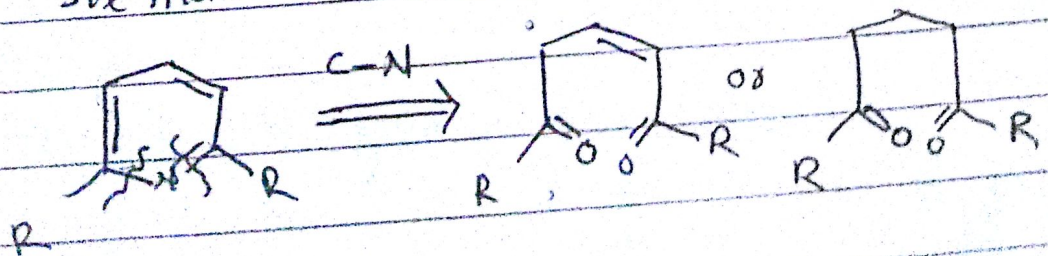
Analysis



Synthesis



Six membered



Design of retrosynthesis of drugs.

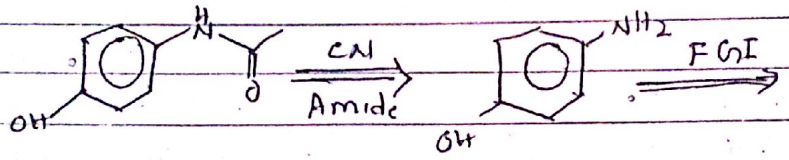
1. Paracetamol,
2. Benzocaine
3. Sulfadrugines
4. Atenolol.

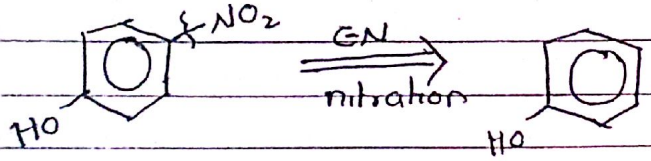
Paracetamol

- The commonly used analgesic paracetamol. is simple amide and should be available by acetylation of P-aminophenol

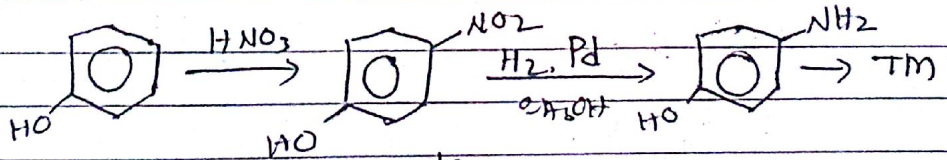
Paracetamol

Analysis



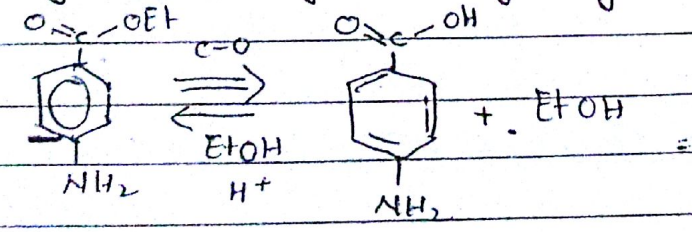


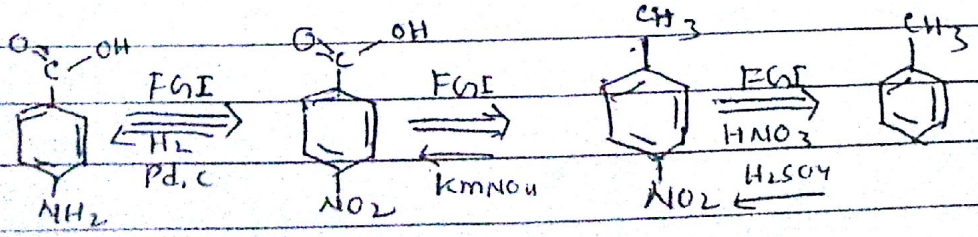
Synthesis :-



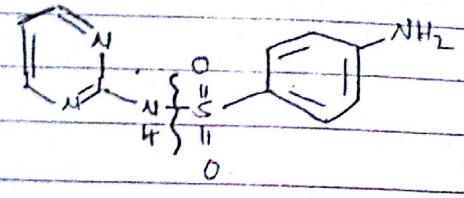
separate from ortho compound

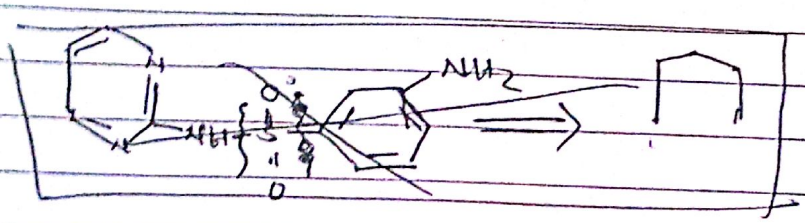
Benzocaine :- synthesis by using FG interconversion

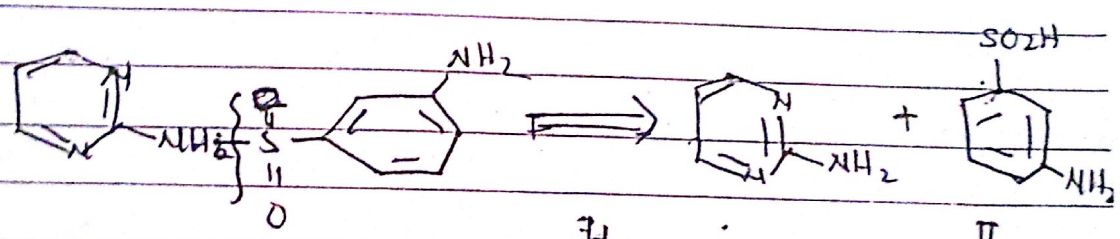


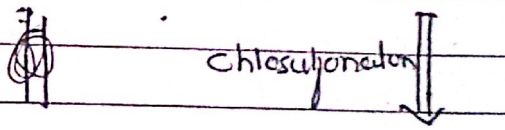


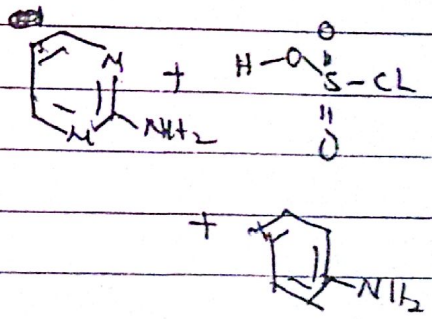
Sulfadiazines :-



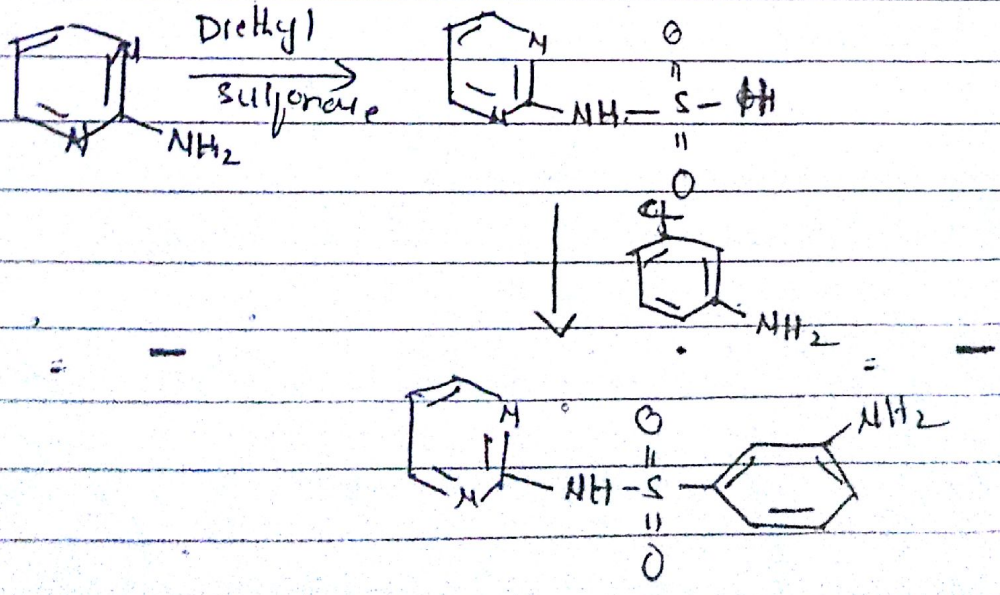




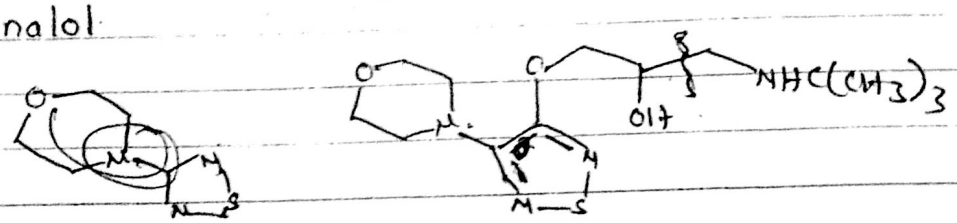


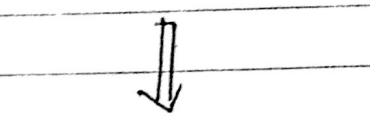


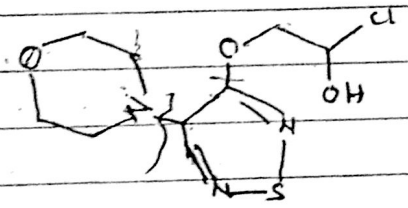
Synthesis would become

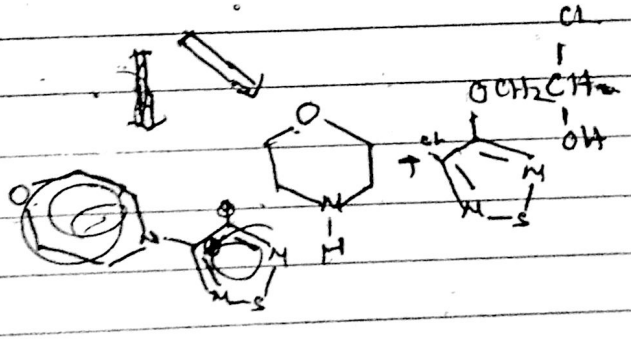


Atenalol









synthesis would be