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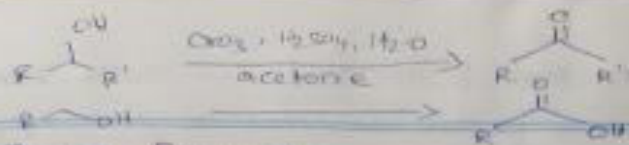
- UNIT III

Oxidation and Reduction Reactions (15 Hours) Study of the following oxidation reactions with mechanism:

Oxidation of alcohols by CrO_3 , DMSO alone, DMSO in combination with DCC; acetic anhydride and oxalyl chloride, oxidation of arylmethane,

oxidation of methylene alpha to carbonyl, allylic oxidation of olefins, oxidative cleavage of glycols, oxidative cleavage of double bonds by ozonolysis.

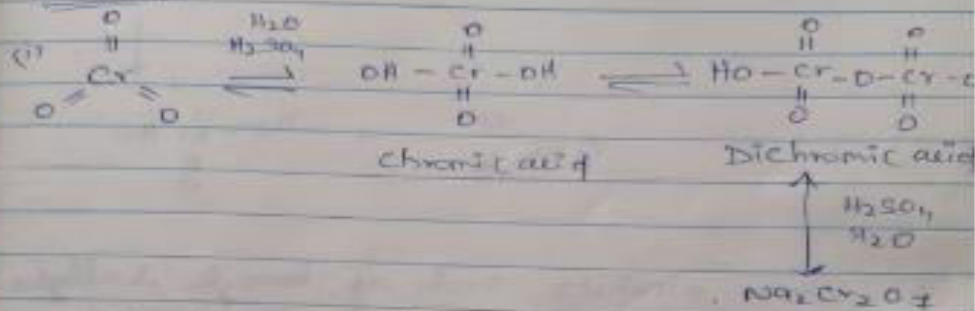
Study of the following reduction reactions with mechanism; Reduction of carbonyl compounds by complex metal hydrides (LAH, NaBH_4 , NaBH_3CN), clemmensen and Wolff Kishner reductions, Birch reduction, MPV reduction.



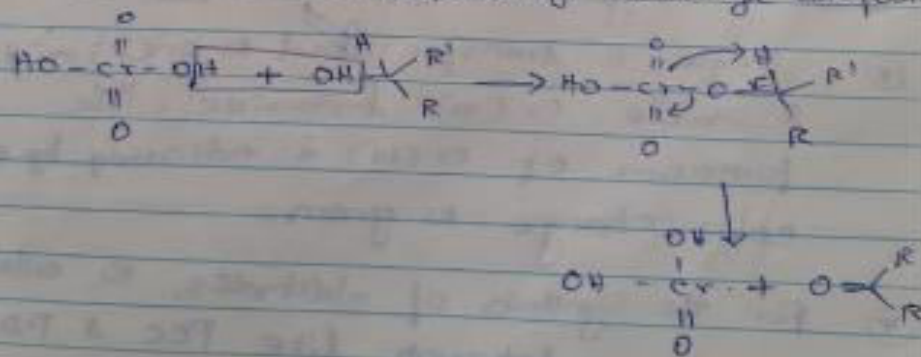
Jones Reagent

It is a mixture of chromium trioxide or sodium dichromate in diluted sulfuric acid which forms chromic acid in situ.

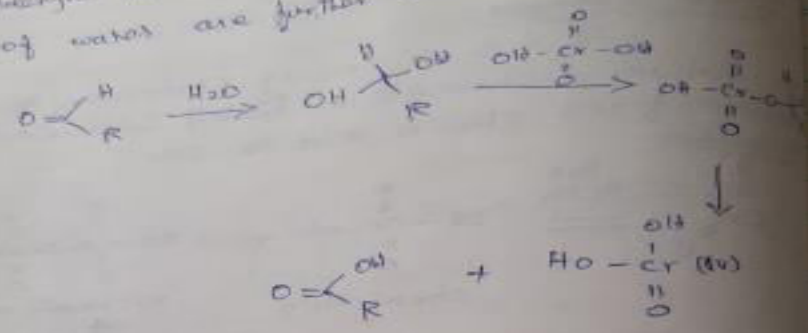
Mechanism:-



(ii) The alcohol & chromic acid form a chromate ester that either reacts intramolecularly or intermolecularly in the presence of a base to yield the corresponding carbonyl compound.



(iii) Aldehyde that can form hydrates in the presence of water are further oxidized to carboxylic acid.

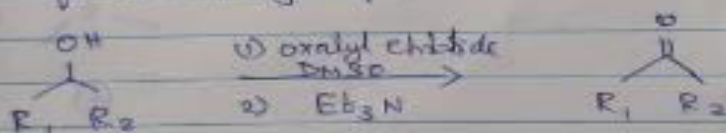


- ⊗ Some alcohols such as benzylic & allylic alcohols give aldehyde that do not form hydrates in significant amount. these can be selectively oxidized with unmodified Jones reagent to yield aldehydes.
- ⊕ Single e⁻ transfer lead to Cr(V) acid & stable Cr(III) hydroxide. The formation of Cr(III) is indicated by a color change to green.
- ⊗ For the synthesis of aldehydes, the Collins reagent reagents like PCC & PDC can be an appropriate choice.

- ⑤ Some newer protocols are available in which a catalytic amount of CrO_3 in aqueous solution is used in tandem with a strong stoichiometric oxidant.

Oxidation of alcohols by DMSO in combination with oxalyl chloride
The Swern oxidation -dt

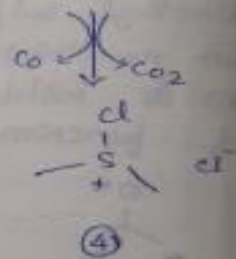
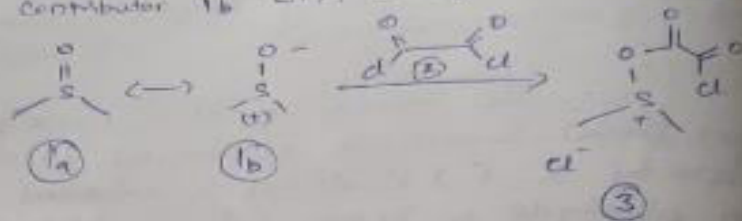
The Swern oxidation, named after Daniel Swern, is a chemical reaction whereby a 1° & 2° alcohol is oxidized to an aldehyde or ketone using oxalyl chloride, dimethyl sulfoxide (DMSO) & an organic base such as triethylamine. The reaction is known for its mild character & wide tolerance of functional groups.



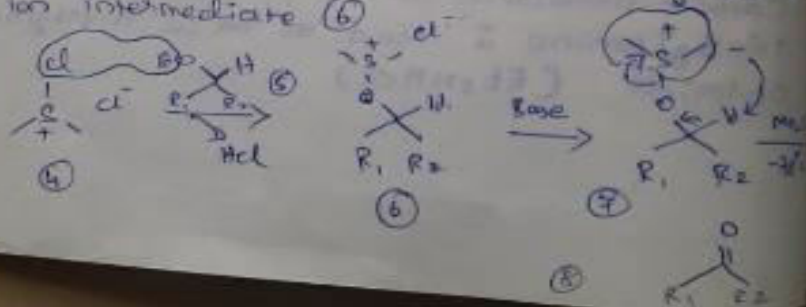
The by-products are Dimethyl sulfide (Me_2S), Carbon monoxide (CO), CO_2 and when triethylamine is used as base triethylammonium chloride (Et_3NHCl)

Mechanism -

i) The first step of the Swain oxidation is the low-temp reaction of dimethyl sulfoxide (DMSO) in a primarily as resonance contributor 1b with oxalyl chloride 2



ii) The chloro-sulfonium chloride (3) reacts with the alcohol (5) to give the key alcoxysulfonium ion intermediate (6)



(ii) The addition of at least 2 equivalents of base typically triethylamine will deprotonate the alkoxy-sulfonium ion to give the sulfur ylide (3)

(iii) The sulfur ylide (3) decomposes to give dimethyl sulfide & the desired ketone

(*) when using oxalyl chloride as the dehydrating agent, the reaction must be kept colder than -60°C to avoid side reactions

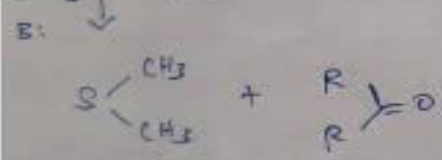
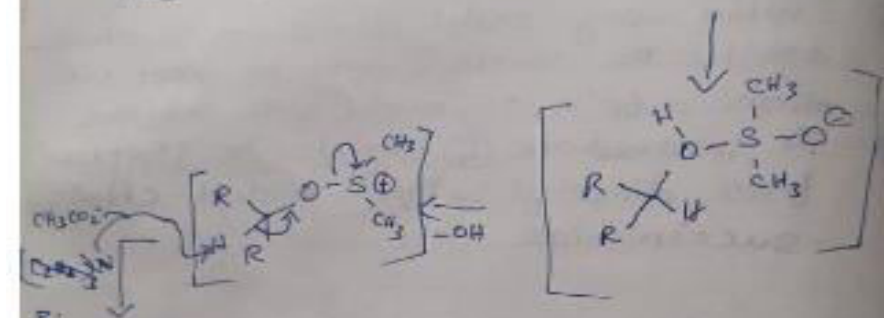
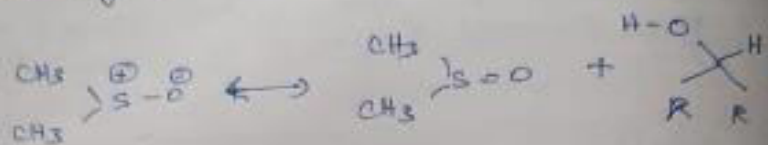
(*) The intermediate (4) can also be prepared from dimethyl sulfide and N-chloro-succinimide

Oxidation of alcohols by DMSO:

The conversion of 1° & 2° alcohols to aldehydes and ketones is an important reaction in which, in its simplest form, can be considered a dehydrogenation (loss of H_2)

By providing an oxygen source to fix the product hydrogen as water. One source of O_2 that has proven effective for the oxidation of alcohols is the simple sulfoxide solvent

DMSO. The alcohol is oxidized; DMSO is reduced to dimethyl sulfide.
 A plausible general mechanism for this interesting & useful reaction is drawn below.



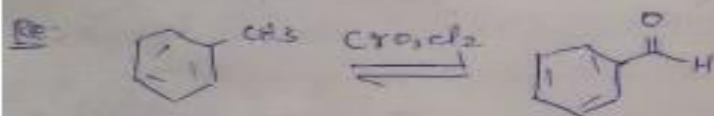
B: = CH_3CO_2^- , CF_3CO_2^- , Cl^- , $(\text{C}_6\text{H}_5)_3\text{N}$

(i) Because so many different electrophile have been used to effect this oxidation, it is difficult to present a single general mechanism.

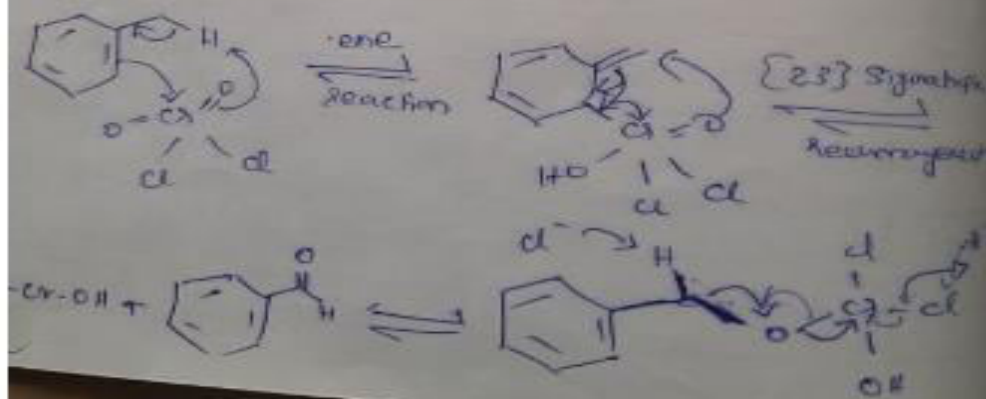
oxidation of arylmethane :-

E'tard reaction :-

The E'tard reaction is a chemical reaction that involves the direct oxidation of an aromatic or heterocyclic bound methyl group to an aldehyde using chromyl chloride. It is named for the French chemist Alexandre Leon E'tard. For ex: toluene can be oxidized to benzaldehyde.



Mechanism:





The reaction mechanism proceeds via an ene reaction with chloral chloride, forming the precipitated Etard reaction complex which is then decomposed by [2,3] sigmatropic rearrangement under reducing conditions to prevent further oxidation to a carboxylic acid.

Reducing conditions for the decomposition of the Etard complex are provided by saturated aq. sodium sulphite.

Typical solvents for the reaction include CS₂, CHCl₃ & CCl₄ with CCl₄ being the most common.

To obtain a highly purified aldehyde product, the Etard complex precipitate is often purified above before decomposition in order to prevent reaction with any unreacted reagent.

The reaction is normally carried out for few days to several weeks & the yields are high.

Limitations:-

- ① The Etard reaction is most commonly used as a relatively easy method of converting toluene into benzaldehyde.

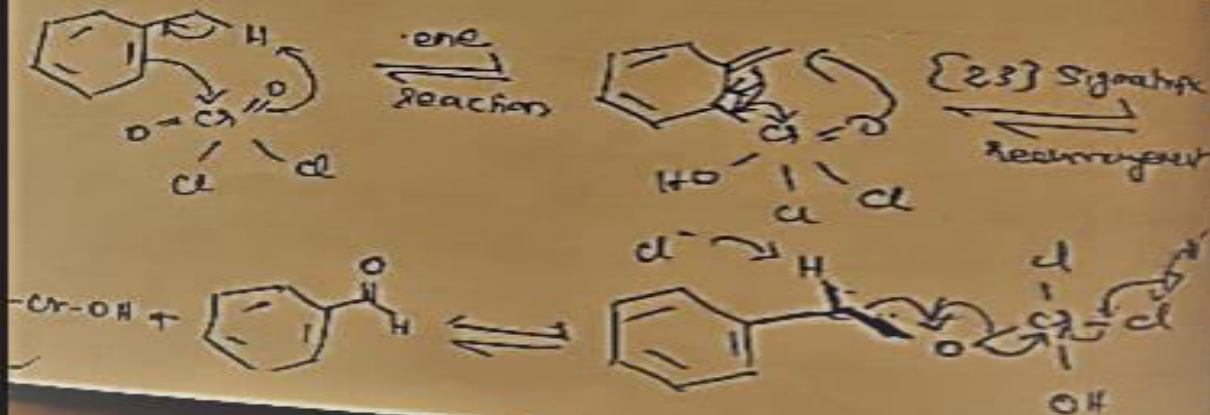
Oxidation of toluene :-

E'tard Reaction :-

The E'tard reaction is a chemical reaction that involves the direct oxidation of an aromatic or heterocyclic bound methyl group to an aldehyde using chromyl chloride. It is named for the French chemist Alexandre Leon E'tard. For ex: toluene can be oxidized to benzaldehyde.



Mechanism :-

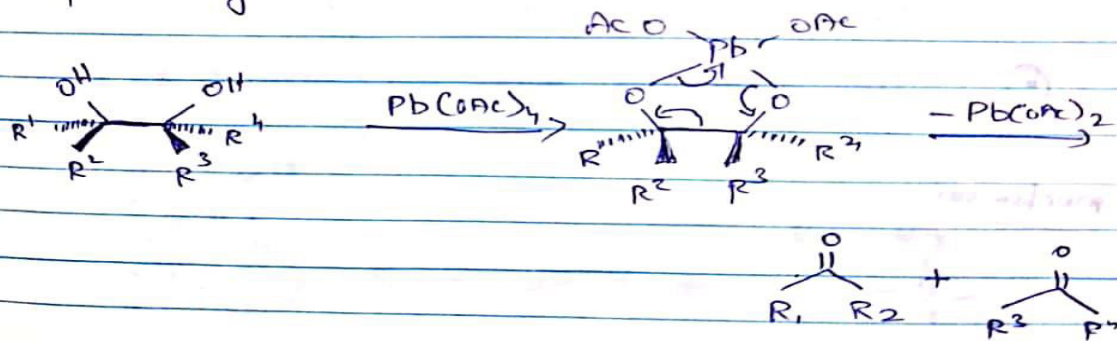


oxidative cleavage of glycols :-

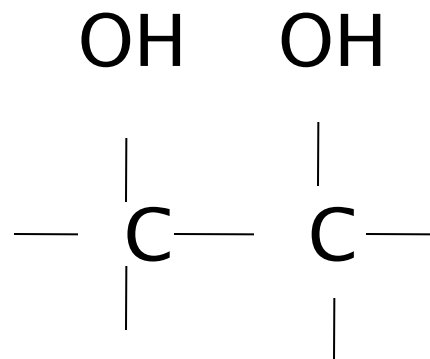
It is a specific type of organic oxidation. The C-C bond in a glycol is cleaved and instead the two oxygen atoms become double bonded to their respective C-atoms. Depending on the substitution pattern in the diol, these carbonyls can be either ketones or aldehydes.

Reagents :-

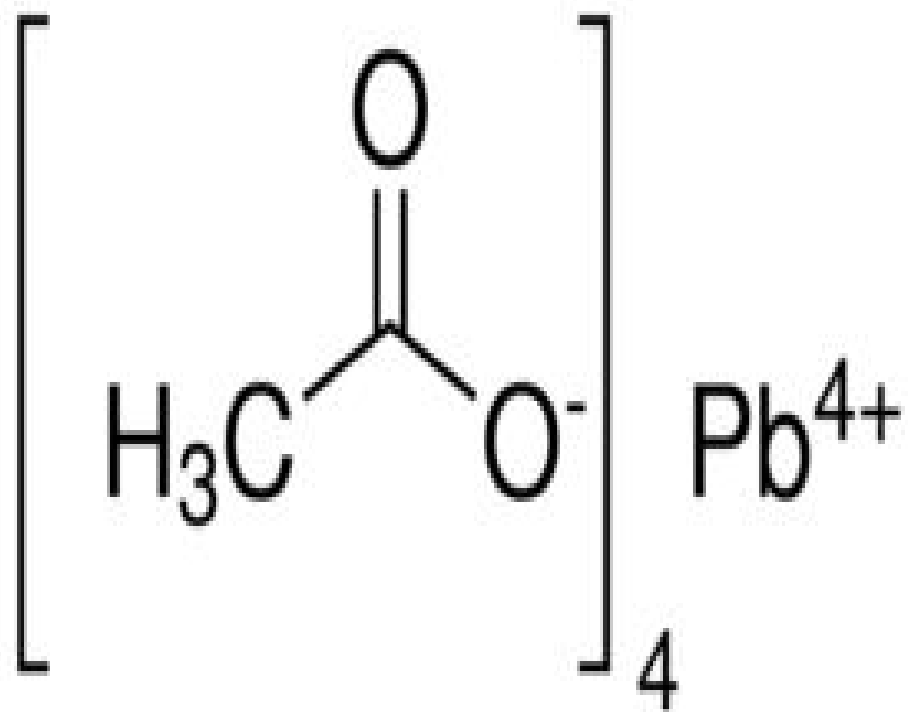
Reagents used in these type of oxidation is periodic acid (HIO_4) & lead tetraacetate ($\text{Pb}(\text{OAc})_4$) are the most common reagents used for glycol cleavage, process called the Criegee oxidation and Malaprade reaction respectively.

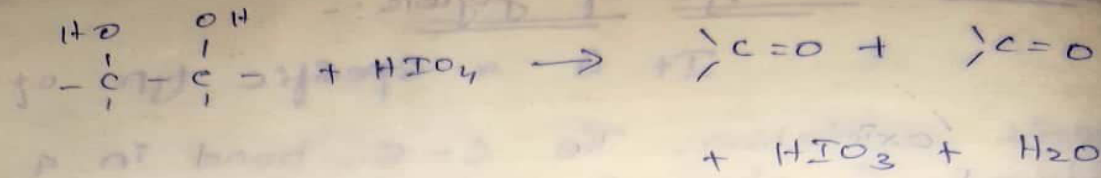


If an R group is a hydrogen atom an aldehyde is formed at that site.
If an R group is a chain that begins with a C-atom, a ketone is formed.



- ▶ HIO_4 – MALAPRADE REACTION
- ▶ $\text{Pb}(\text{OAc})_4$ – CRIGEE REACTION





① 1,2 (or) vicinal diols are cleaved by periodic acid, HIO_4 into two carbonyl compounds

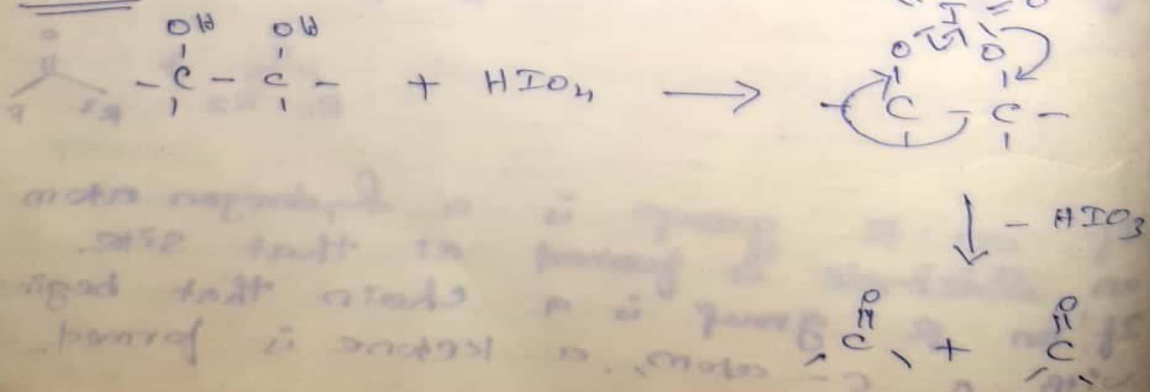
② The reaction is selective for 1,2 diols

③ The reaction occurs via the formation of a cyclic periodate ester

④ This can be used as a functional group test for 1,2 diols

⑤ The products are determined by the substituents on the diol.

Mechanism:-

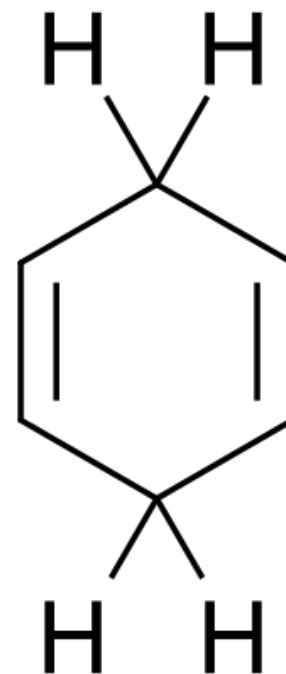
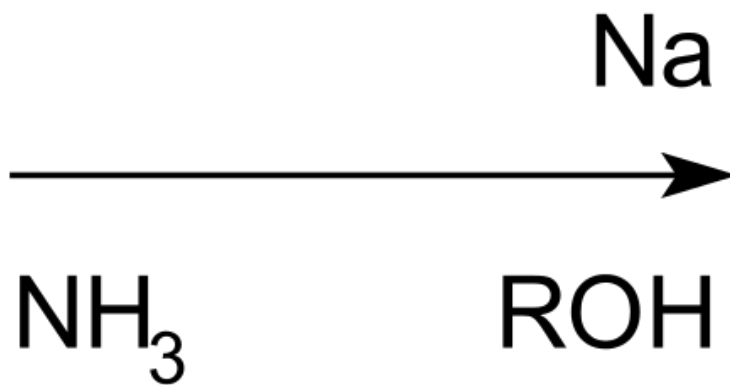
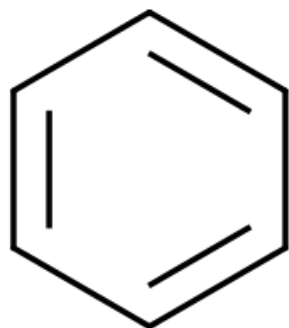


Birch reduction

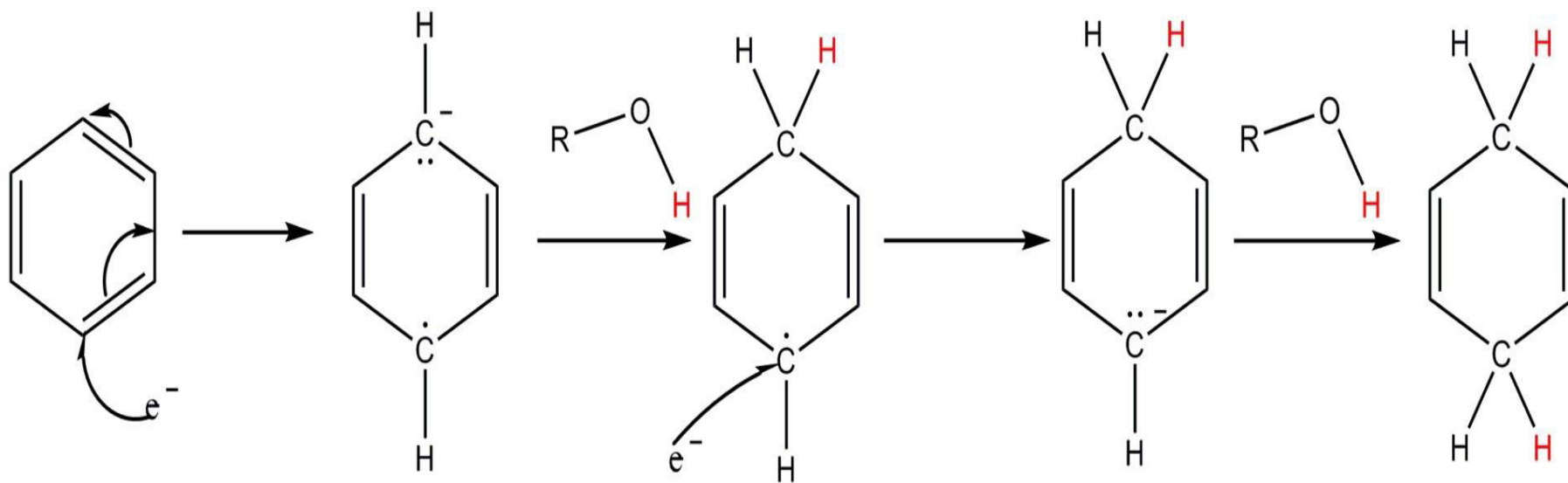
- ▶ The **Birch reduction** is an organic reaction that is used to convert arenes to cyclohexadienes. The reaction is named after the Australian chemist Arthur Birch. In this organic reduction of aromatic rings in liquid ammonia with sodium, lithium, or potassium and an alcohol, such as ethanol and tert-butanol. This reaction is unlike catalytic hydrogenation, which usually reduces the aromatic ring all the way to a cyclohexane.



Aromatic ring to cyclohexane

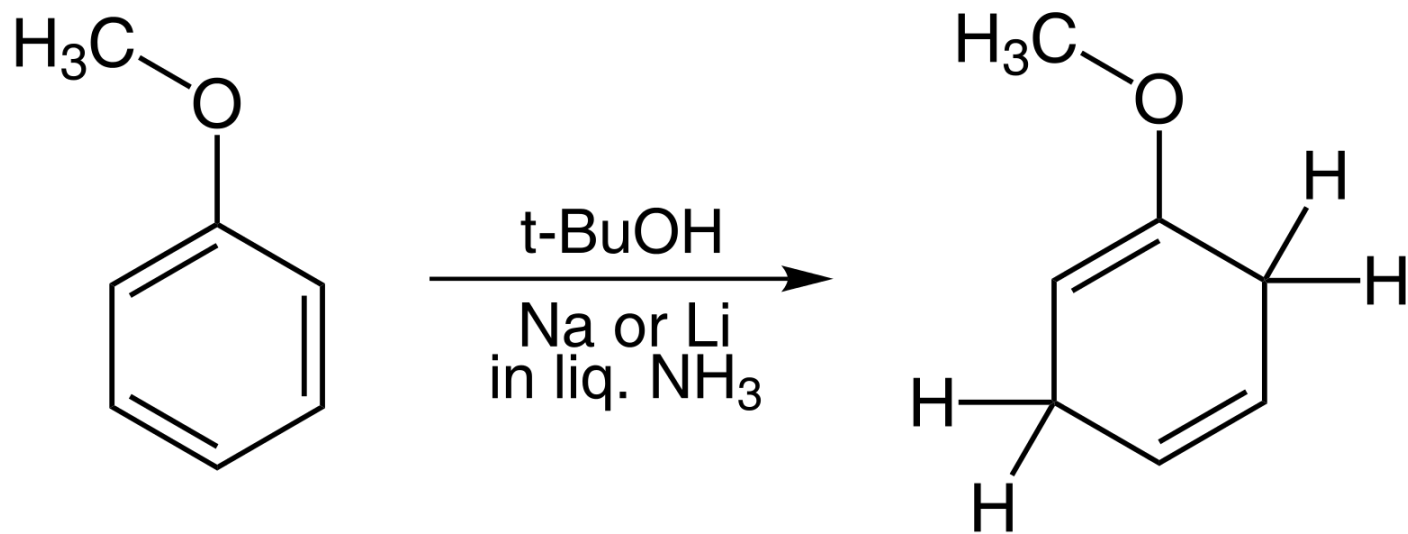


MECHANISM



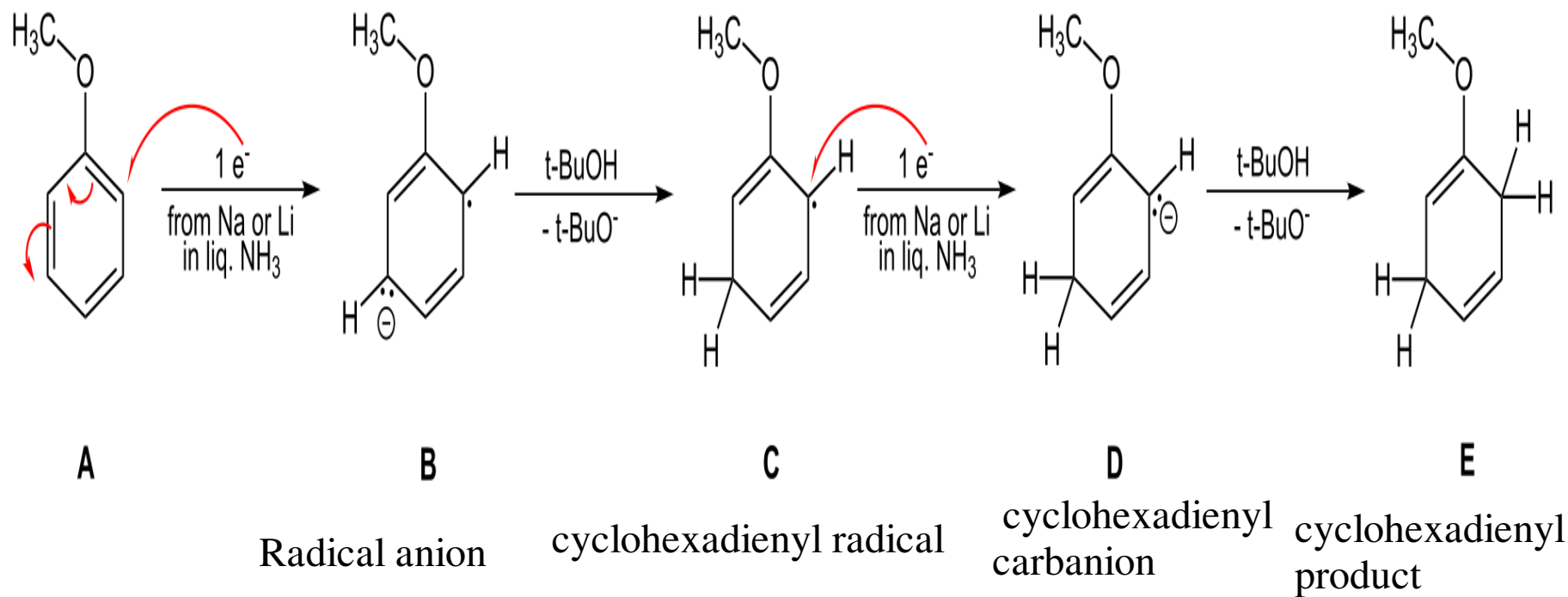
The solvated electrons add to the aromatic ring to give a radical anion. The added alcohol supplies a proton to the radical anion and also to the penultimate carbanion; for most substrates ammonia is not acidic enough.

BIRCH reduction of anisole



(1)

MECHANISM

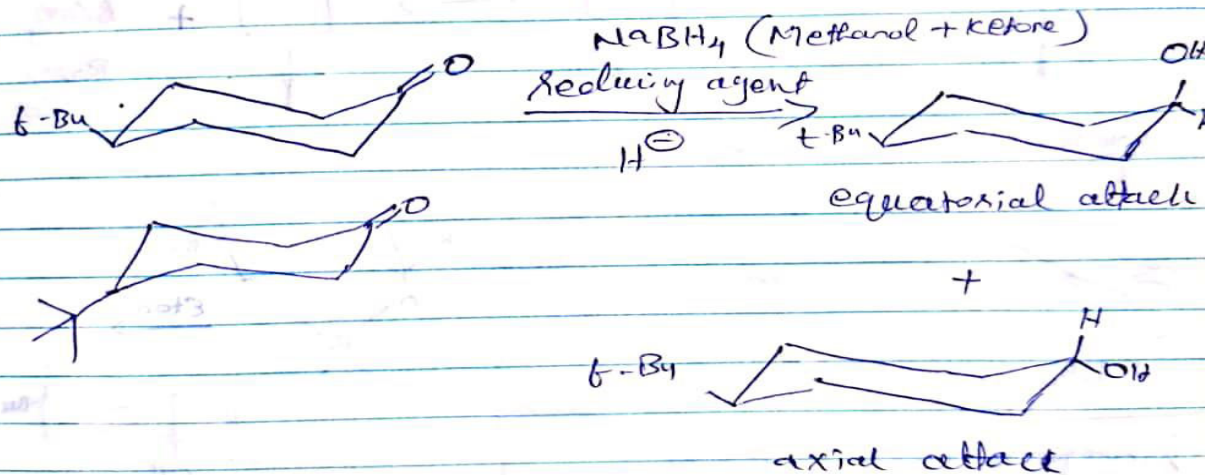


- ▶ The solution of metal in ammonia provides electrons which are taken up by the aromatic ring to form the corresponding radical anion B in the first step of the reaction.
- ▶ This is followed by protonation by the alcohol to form a cyclohexadienyl radical C. Next, a second electron is transferred to the radical to form a cyclohexadienyl carbanion D. In the last step a second proton leads the cyclohexadienyl carbanion to the unconjugated cyclohexadienyl product. These steps are outlined below for the case of anisole.

Bisch Reduction :-

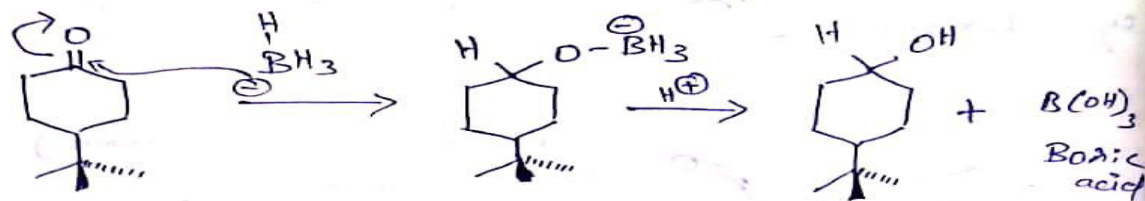
The Birsch reduction is an organic reaction which is particularly useful in synthetic organic chemistry. It converts aromatic compounds having a benzenoid ring into a product 1,4-cyclohexadiene.

Stereoselective Reduction of 4-tert-Butyl cyclohexanone :-

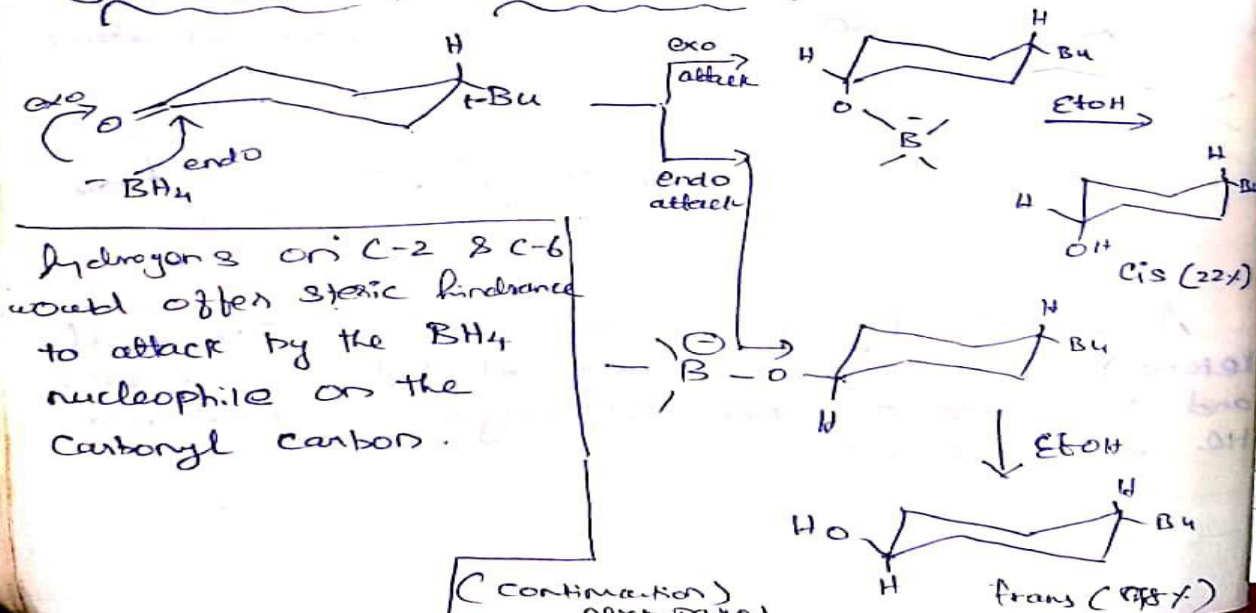


Asymmetrically substituted ketones (prochiral ketones) provide secondary alcohols on reduction and introduce a new stereogenic centre into the molecule.

In general sodium borohydride is able to reduce ketones and aldehydes with good chemoselectivity over other carbonyl compounds. In the reduction of 4-tert-butylcyclohexanone, the stereoselectivity of sodium borohydride is studied by interpretation of the $^1\text{H-NMR}$ spectrum of the product. Mechanism:



Stereochemical considerations:



Reduction of carbonyl compounds by hydrides:-

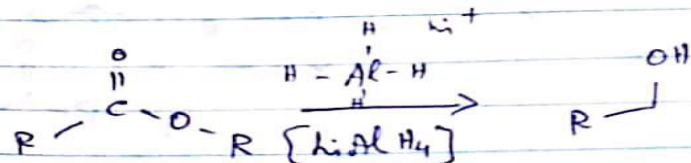
(i) Hydride reduction:-

(*) Carbonyl reduction is the organic reduction of any carbonyl group by a reducing agent. Typical carbonyl compounds are ketones, aldehydes, carboxylic acids, esters & acid halides.

(*) Carboxylic acids, esters and acid halides can be reduced to either aldehydes or a step further to primary alcohols, depending on the strength of the reducing agent.

(*) Metal hydrides based on boron and aluminium are common reducing agents; catalytic hydrogenation is also an important method of reducing carbonyls.

(*) Before the discovery of soluble hydride reagents, esters were reduced by the Bouveault-Blanc reduction employing a mixture of sodium metal in the presence of alcohols.



The most common sources of the hydride nucleophile are lithium aluminium hydride (LiAlH_4) and

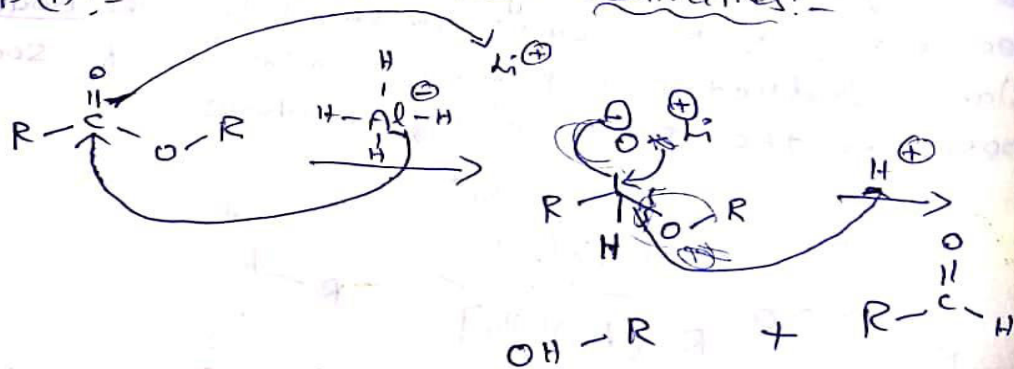
Sodium borohydride (NaBH_4). The hydride anion is not present during this reaction; rather, these reagents serve as a source of hydride due to the presence of a polar metal-hydrogen bond.

mechanism:

The reaction mechanism for metal hydride reduction is based on nucleophilic addition of hydride to the carbonyl carbon.

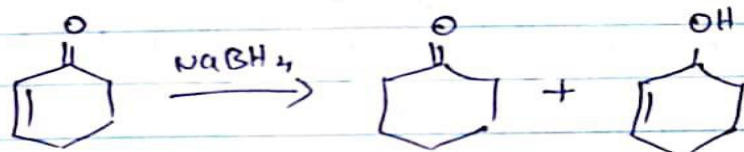
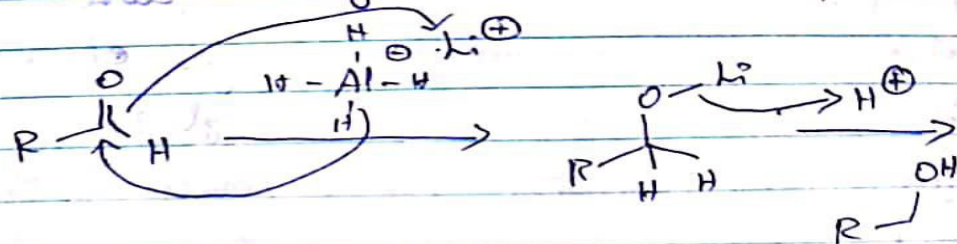
In some cases, the alkali metal cation, especially Li^+ activates the carbonyl group by coordinating to the carbonyl oxygen, thereby enhancing the electrophilicity of the carbonyl.

Reduction of carboxylic acid derivatives:
 step (i) :-



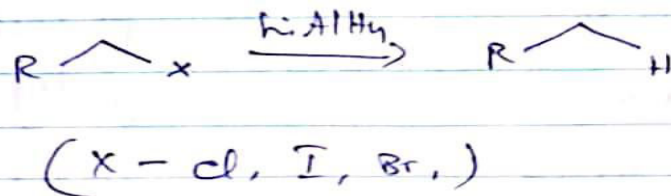
For reduction of aldehydes and ketones:-
 Here an aluminium hydride ion

reduces the compound to form an alkoxide salt. After the complete reduction, the alkoxide is protonated to give the alcohol product.

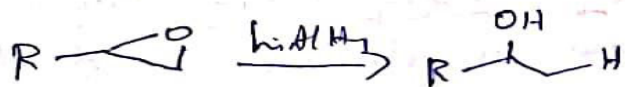


The above NaBH₄ reduction of an enone shows two possible products;

Reduction of halides & sulfonates:-



Epoxyde ring opening:-

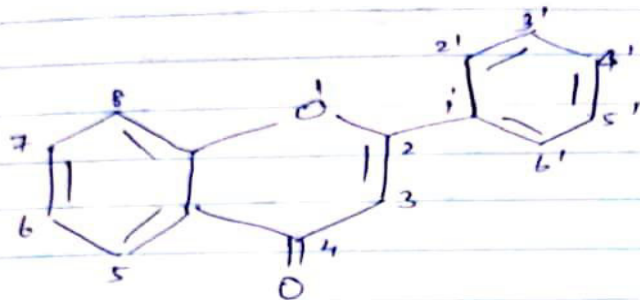


Due to the large size of the t-butyl group, the molecule 4-t-butylcyclohexanone exist almost exclusively in one chair conformation the one in which the t-butyl gp is in the equatorial position. As a result of this conformational immobility of the molecule, the sodiumborohydride reduction of 4-t-butylcyclohexanone from one side of the molecule gives trans-4-t-butylcyclohexanol as the major product, whereas the reduction from the other side of the molecule give cis-4-t-butylcyclohexanol as the minor product.

The Identity & Percent of each Stereoisomer present in the product mixture are established easily by Proton NMR. (3 peaks 1.9, 1.7, 1.5) (equatorial proton)
 (5 peaks 1.3) (axial-down field)

As expected, for t-butylcyclohexanone the bull's eye is on the carbonyl carbon. But more importantly, when the exoside of the molecule is viewed it appears ^{that} the axial

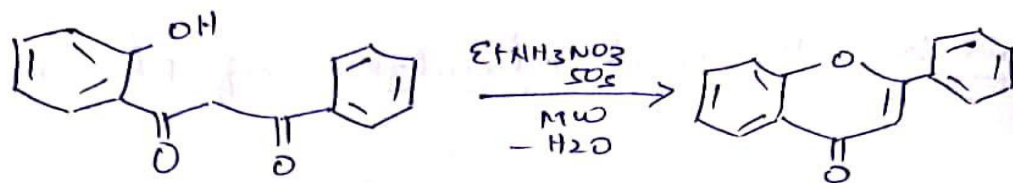
Synthesis & Structural elucidation of Flavones:-



Molecular Structure of the flavone

- ① Flavones (flame - yellow) are a class of flavonoids based on the backbone of 2-phenyl chromen-4-one (2-phenyl-1-benzopyran-4-one)
- ② Flavones are mainly found in cereals and herbs.
- ③ Several methods exist for the synthesis of flavones:
 - ① The Allan - Robinson reaction
 - ② The Auwers synthesis
 - ③ The Baker - Venkataraman rearrangement
 - ④ The Algar - Flynn - Yamada reaction

Another method is the dehydrative cyclization of certain 1,3-diaryl diketones.



81%

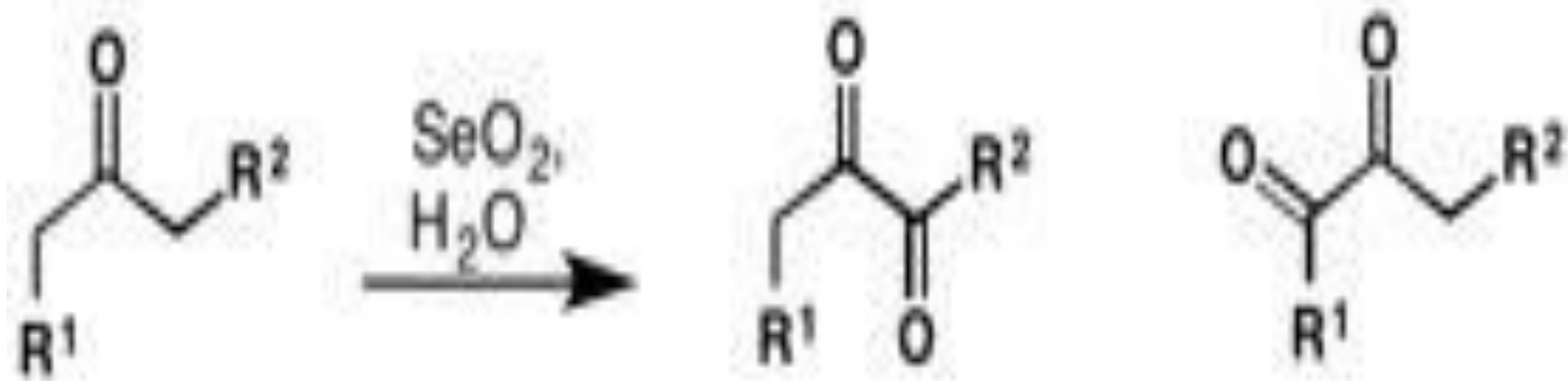
This particular study making use of an ionic liquid solvent and microwave irradiation

Wessely - Moses Rearrangement :-

The W.M. rearrangement has been an important tool in structure elucidation of flavonoids. It involves the conversion of 5,7,8-trimethoxyflavone into 5,6,7-trihydroxyflavone on hydrolysis of the methoxy groups to phenol groups. It also has synthetic potential for example

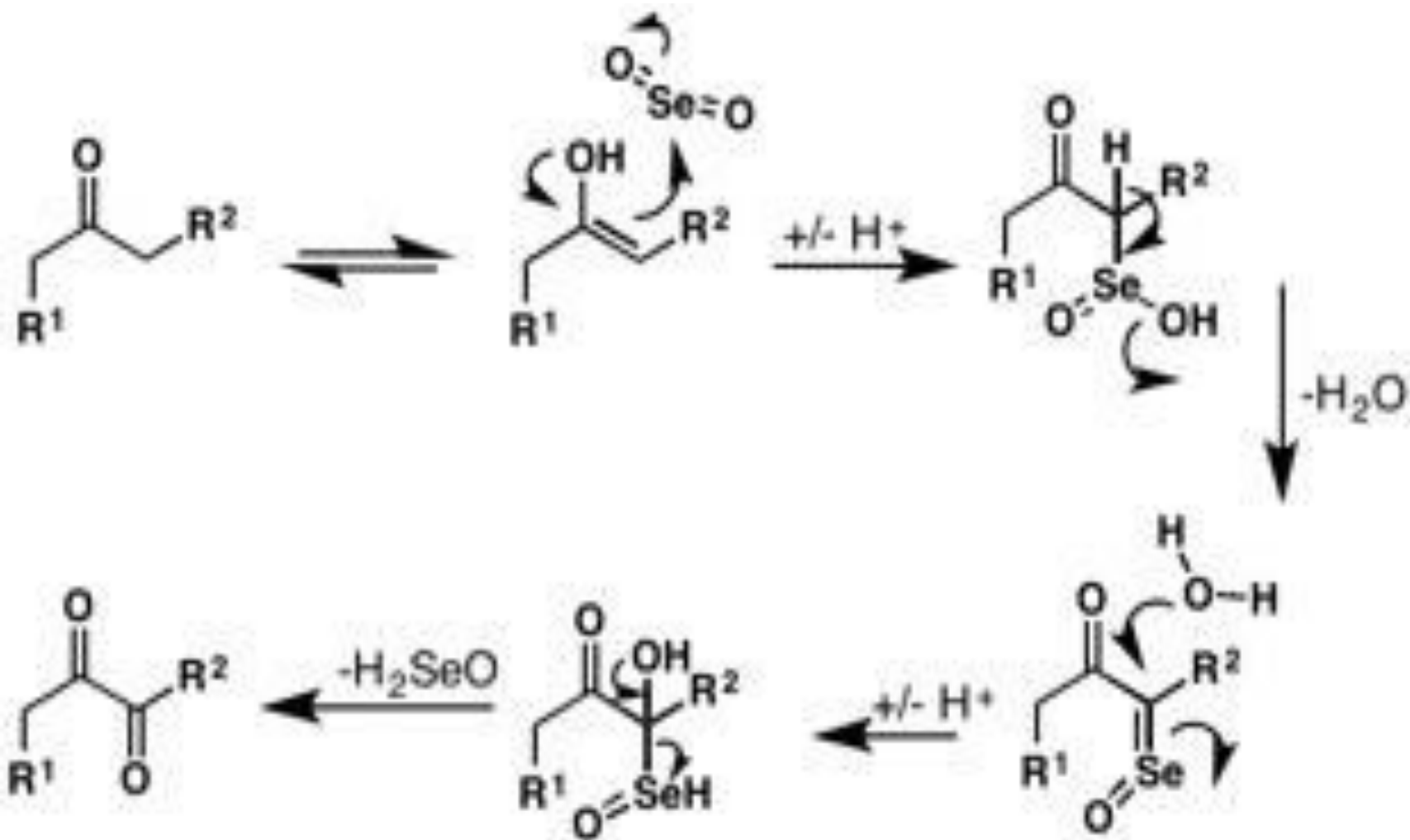
Allylic oxidation of olefins

- ▶ **The Riley oxidation** is a selenium dioxide-mediated oxidation of methylene groups adjacent to carbonyls. It was first reported by Riley and co-workers in 1932. ... Today, selenium-dioxide-mediated oxidation of methylene groups to alpha ketones and at the allylic position of olefins is known as the Riley Oxidation.

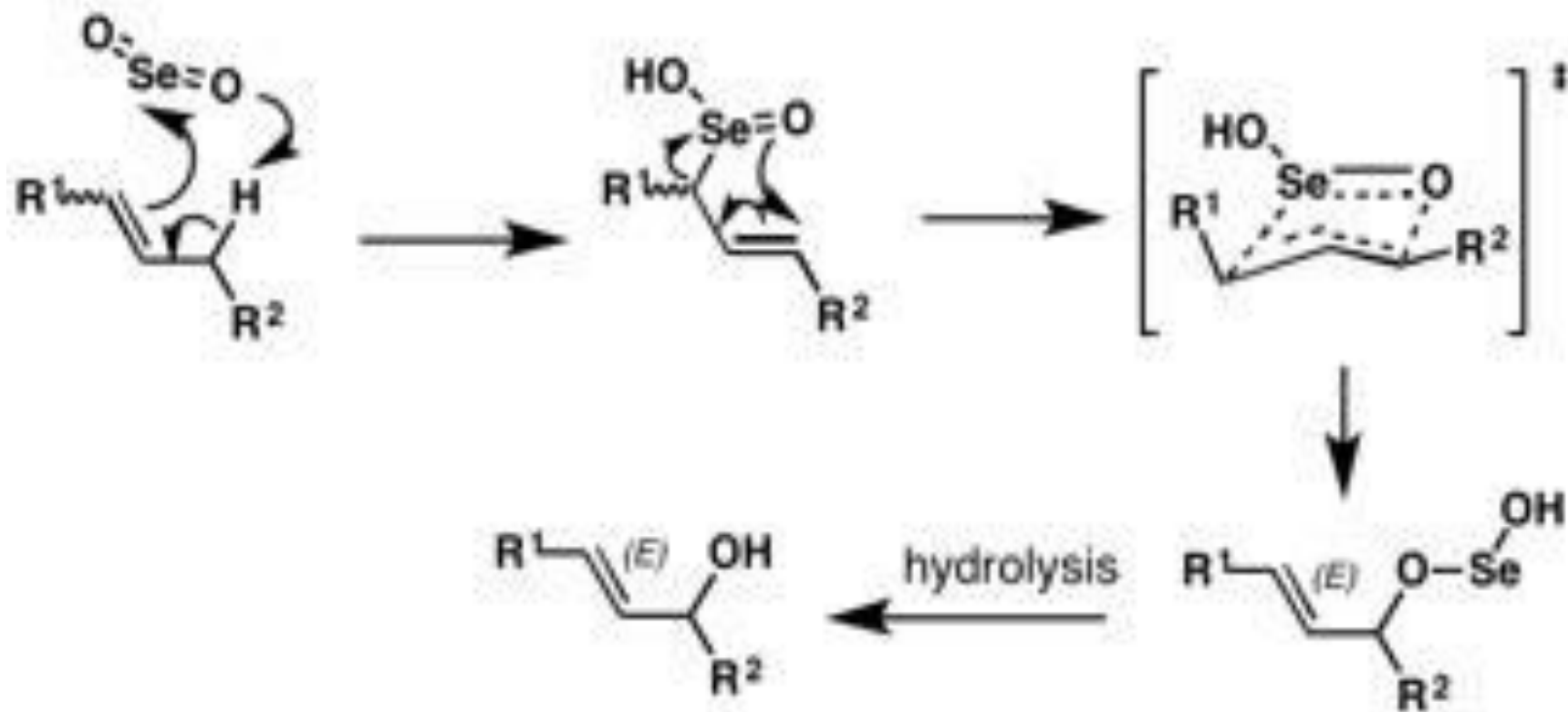


MECHANISM

- ▶ The mechanism of oxidation of $-\text{CH}_2\text{C}(\text{O})\text{R}$ group by SeO_2 has been well investigated. The oxidation of carbonyl alpha methylene positions begins with attack by the enol tautomer at the electrophilic selenium center. Following rearrangement and loss of water, a second equivalent of water attacks the alpha position. Selenic acid is liberated in the final step to give the 1,2-dicarbonyl product.



- ▶ Allylic oxidation using selenium-dioxide proceeds via an ene reaction at the electrophilic selenium center. A 2,3-sigmatropic shift, proceeding through an envelope-like transition state, gives the allylselenite ester, which upon hydrolysis gives the allylic alcohol. The (*E*)- orientation about the double bond, a consequence of the envelope-like transition state, is observed in the penultimate ester formation, is retained during the hydrolysis step giving the (*E*)-allylic alcohol product.^[4]



Application

- ▶ Selenium-dioxide mediated oxidation was used in the synthesis of the diterpenoid ryanodol.
 - ▶ Selenium dioxide mediated allylic oxidation to access ingenol.
- 