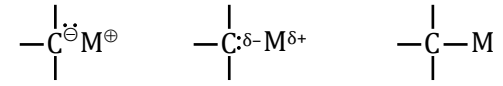
04 Grignard's Reagent

INTRODUCTION

Compounds that contain carbon–metal (M—C) bonds are called **organometallic compounds**. Carbon–sodium and carbon–potassium are largely ionic in character; carbon–tin, carbon-lead and carbon-mercury bonds are covalent. Carbon–lithium and carbon-magnesium bonds lie between them.



Ionic (M = Na^+, K^+) | (M = Mg and Li) | Covalent (M = Hg, pb, Sn, or Tl)

The reactivity of organometallic compounds increases with the increase in percent ionic character of C—M bond. Alkylsodium and alkylpotassium compounds are highly reactive and are among the most powerful bases. Organomercury and organolead compounds are less reactive, poisonous, and soluble in non-polar solvents.

Organolithium and organomagnesium compounds are of great importance in organic synthesis and relatively less stable in ether solutions because of their ionic nature. The C atom in them is a strong base and a strong nucleophile.

Organolithium compounds are prepared by the reduction of RX with lithium metal in dry ether solvent (diethyl ether, Et_2O, and THF, tetrahydrofuran ).

$$RX + 2Li \xrightarrow[-10^\circ C]{THF} RLi + LiX$$

$$ArX + 2Li \xrightarrow{THF} ArLi + LiX$$

The order of reactivity of RX is RI > RBr > RCl.

GRIGNARD REAGENTS

Organomagnesium halides were discovered by French chemist Victor Grignard in 1900. Grignard received the Nobel prize for his discovery in 1912 and organomagnesium halides are now called Grignard reagents (G.R.) in his honour.

PREPARATION OF GRIGNARD REAGENTS

G.R. are prepared by the reaction of organic halide (RX) with Mg in dry ether solvent.

$$RX + Mg \xrightarrow[\Delta]{\text{Diethyl ether}} RMgX$$

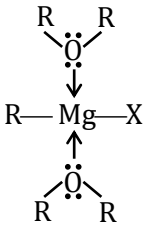
$$ArX + Mg \xrightarrow[\Delta]{Et_2O} ArMgX$$

The order of reactivity of halides with Mg is:

RI > RBr > RCl

ArMgX are more easily prepared from ArBr and ArI than from ArCl.

G.R. form a complex with ether solvent and formation of this complex imparts stability to G.R.



The method (which can be used for 1°, 2°, and 3° alcohols) is little used in practice, since an alkyl halide can be converted into the corresponding alcohols.

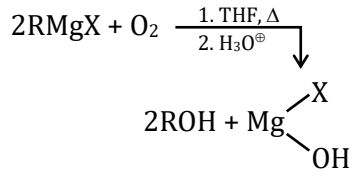
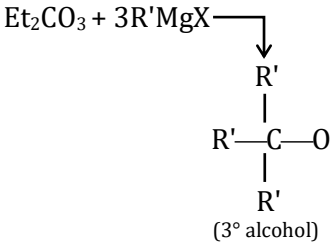
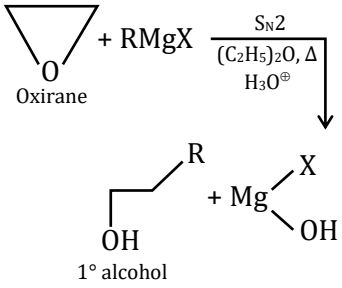
SYNTHESIS OF ALKANES, ALKENES ALKYNES, ALCOHOLS, CARBONYL COMPOUNDS

Synthesis of alcohols, aldehydes, ketones, acids, amines, esters, cyanides, thiols, dithionic acids, sulphonic acid, alkyl iodides, organometallic compounds, etc., are given below.

REACTIONS OF GRIGNARD REAGENTS (SYNTHESIS OF ALCOHOLS)

Table 1.1: Summary of synthesis of alcohols by Grignard Reagent

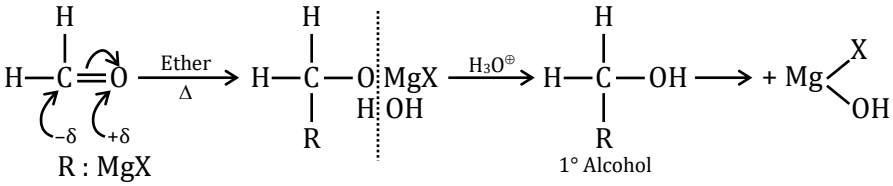
	Aldehyde and Ketone method (I)	Ester method (II)	Anhydride method (III)	Acid halide method (IV)
1.	$RCHO + R'MgX \rightarrow RCHOH(R')$ (2° alcohol) One R value comes from aldehyde and One R' value comes from R'MgX when HCHO react with RMgX, 1° alcohol is formed.	$HCOOR + 2R'MgX \rightarrow R'CH(OH)R'$ (2° alcohol) (formic ester) Two R' value comes from R'MgX	$HCOOCOH + R'MgX \rightarrow R'CH(OH)R'$ (2° alcohol) (Formic or methanoic anhydride) Two R' value comes from R'MgX	$HCOX + R'MgX \rightarrow R'CH(OH)R'$ (2° alcohol) (Formyl halide) Two R' value comes from R'MgX
2.	$R_2C{=}O + R'MgX \rightarrow R_2R'C{-}OH$ (3° alcohol) Two R value comes from ketone and one R' value comes from R'MgX	$RCOOR' + 2R'' \rightarrow RR''_2C{-}OH$ (3° alcohol) (Ester) One R value comes from ester and two R'' value comes from R''MgX	$RCOOCOR' + 2R'' \rightarrow RR''_2C{-}OH$ (3° alcohol) (Anhydride) One R value comes from anhydride and two R'' value comes from R''MgX	$RCOX + 2R'MgX \rightarrow RR'_2C{-}OH$ (3° alcohol) (Acid halide) One R value comes from acid halide and two R' value comes from R'MgX

With O_2 (V)	Diethyl carbonate method (VI)	With cyclic ethers (VII)
	 Three value of R' comes from R'MgX	

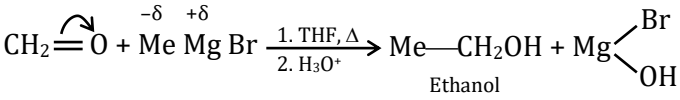
I. From aldehydes and ketones

G.R. react with carbonyl compound to give 1°,2° and 3° alcohol.

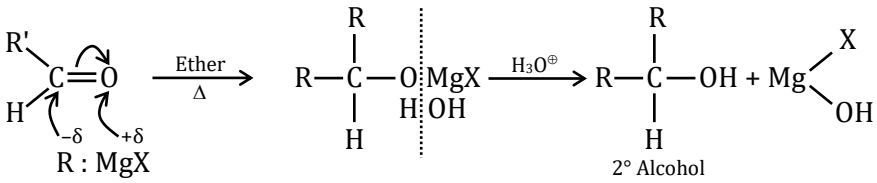
a. G.R. react with formaldehyde (methanal, HCHO) to give 1° alcohol.



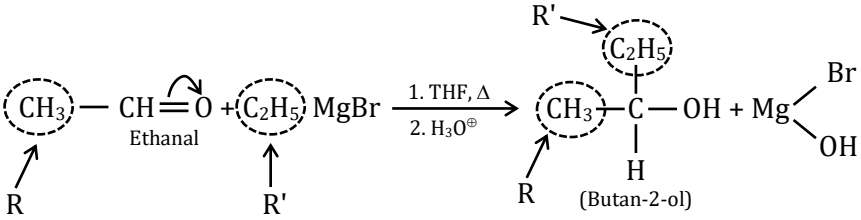
For example:



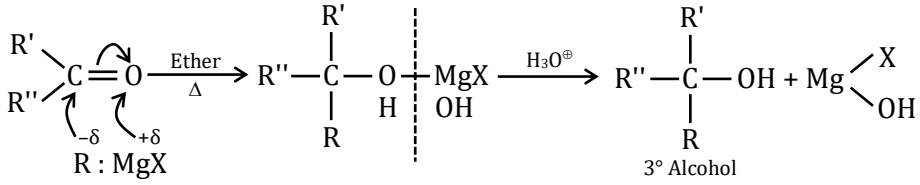
b. G.R. react with all other aldehydes to give 2° alcohols.



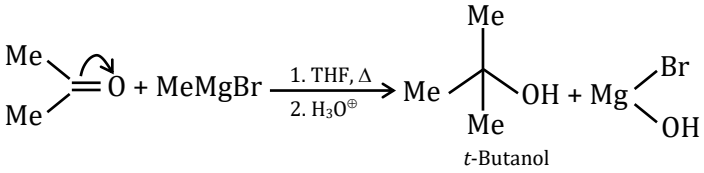
For example:



c. G.R. react with ketones to give 3° alcohols.

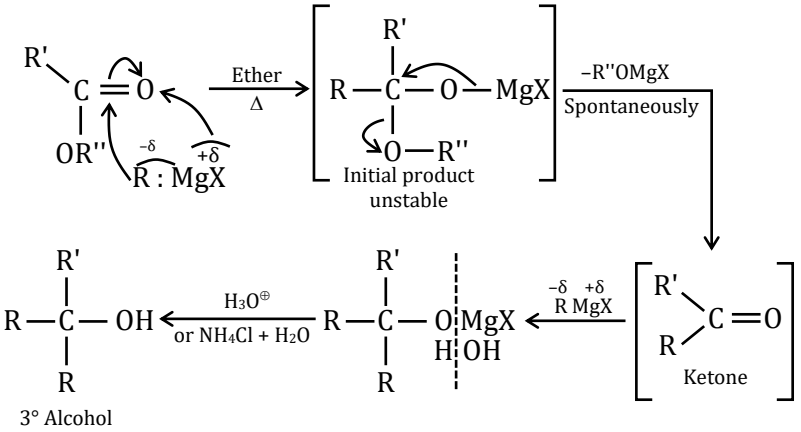


For example:

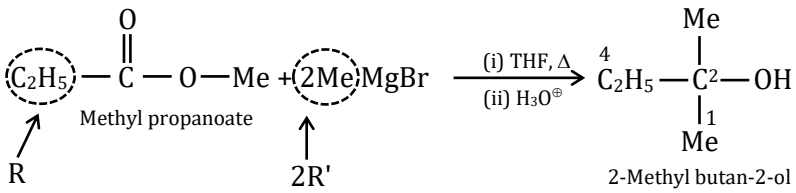


d. Two moles of G.R. reacts with esters to give 3° alcohols.

One mole of G.R. reacts with esters to form ketones. Ketones are more reactive towards G.R. than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of G.R. After hydrolysis, the product is 3° alcohol, with two same alkyl groups that correspond to the alkyl portion of the G.R.



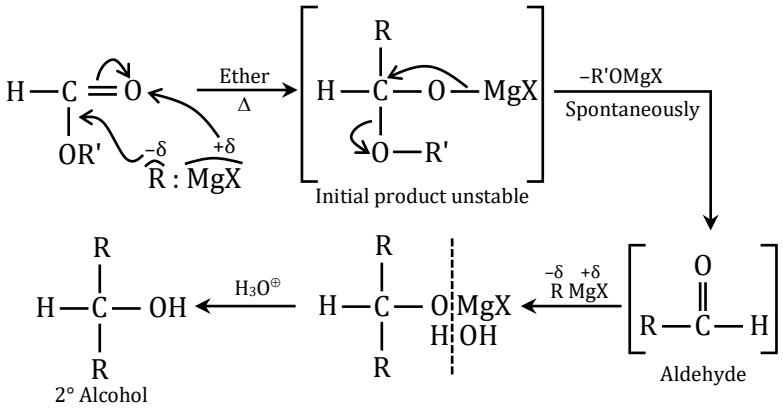
For example:



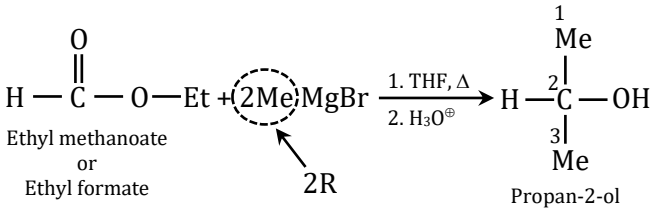
II. Ester method

a. Two moles of G.R. reacts with formic ester or methanoic ester ($H-\overset{O}{\overset{\|}{C}}-OR$) to form an aldehyde. Aldehyde are more reactive than formic esters towards G.R. Therefore, as soon as a molecule of the aldehyde is formed during the hydrolysis, it further reacts with G.R.; The product formed is 2° alcohol, containing two same alkyl groups that correspond to the alkyl portion of the G.R.

Only 2° alcohol containing two same alkyl groups can be prepared by this method:

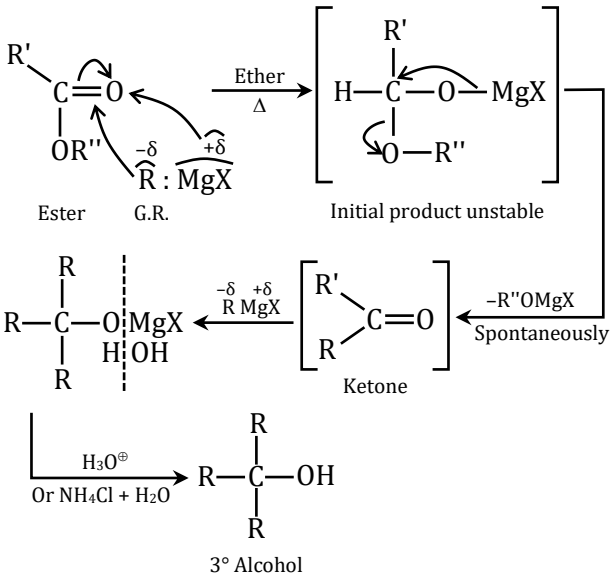


For example:

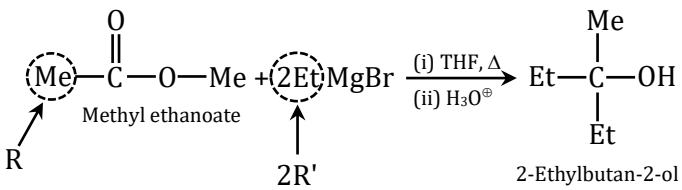


b. Two moles of G.R. react with esters to give 3° alcohols.

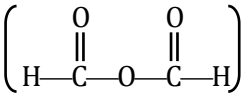
One mole of G.R. reacts with esters to form ketones. Ketones are more reactive towards G.R. than esters. Therefore, as soon as a molecule of the ketone is formed in the mixture, it reacts with a second molecule of G.R. After hydrolysis, the product is 3° alcohol, with two same alkyl groups that correspond to the alkyl portion of the G.R.



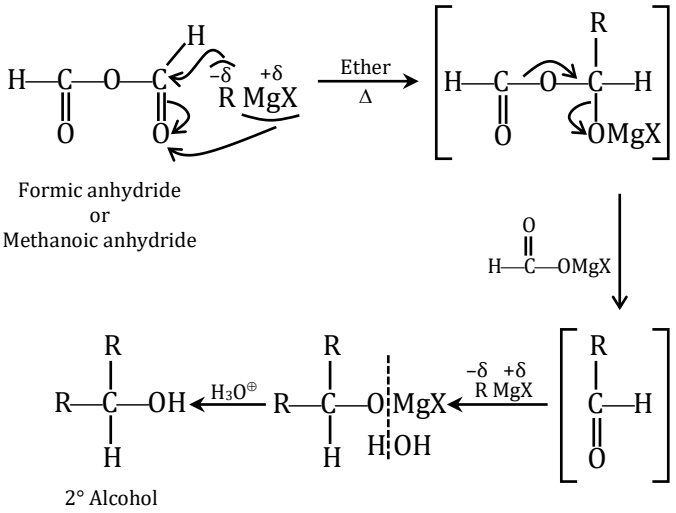
For example:



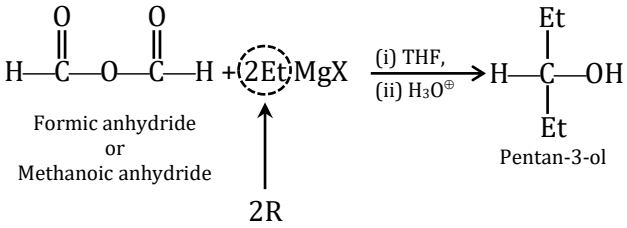
III. Anhydride method

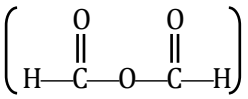
a. Two moles of G.R. reacts with methanoic or formic anhydride  to give 2° alcohol, with two same alkyl groups that correspond to the alkyl portion of the G.R.

Only 2° alcohols containing two same alkyl groups can be prepared by this method.

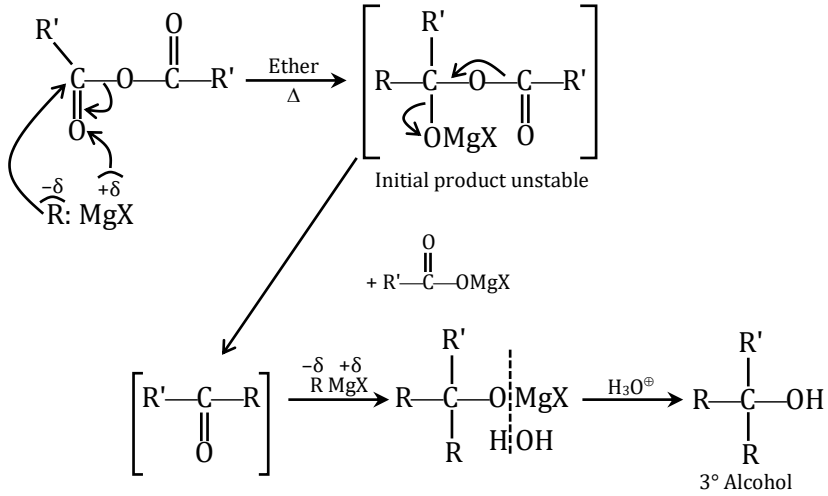


For example:



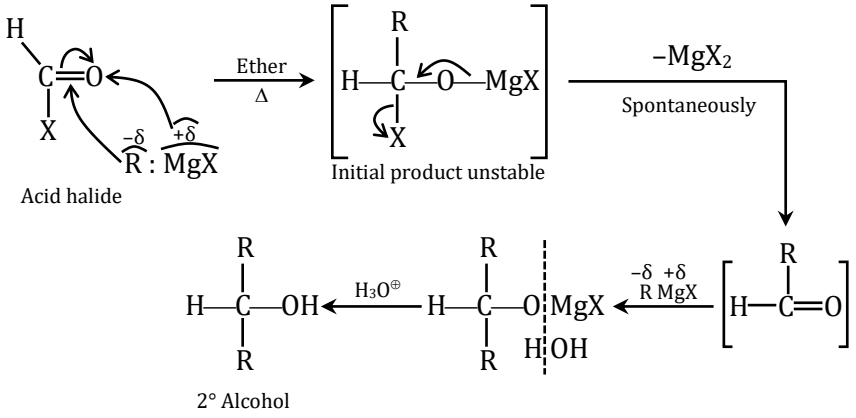
b. Two moles of G.R. reacts with acid anhydride  to give 3° alcohol.

Acid anhydrides react in the same way as ester, and halides react with RMgX.



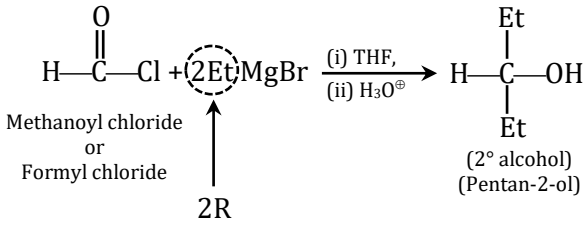
IV. Acid halide method

a. Two moles of G.R. reacts with formyl halides or methanoyl halides $\left(\begin{array}{c}O\\ \|\\ H-C-X\end{array}\right)$ to give 2° alcohols, with two same alkyl groups that correspond to the alkyl portion of the G.R.



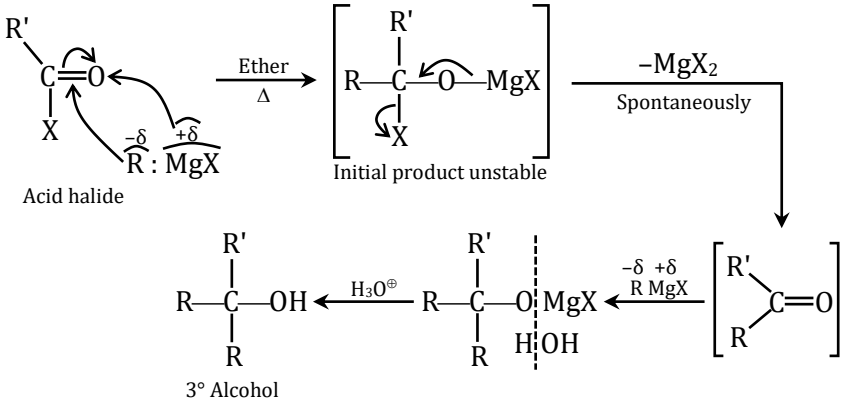
Methanoyl or formyl chloride is an unstable compound, but it prepared in *situ* (inside the reaction) and reacts with RMgX.

For example:

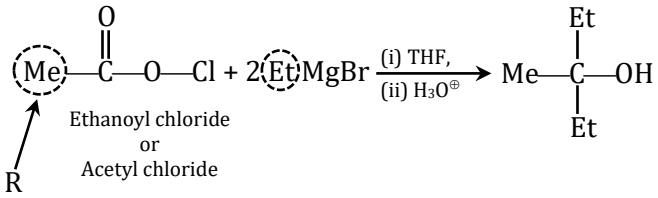


b. Two moles of G.R. reacts with acid halides $\left(\begin{array}{c}O\\ \|\\ R-C-X\end{array}\right)$ to give 3° alcohols.

One mole of G.R. reacts with acid halides. $\left(\begin{array}{c}O\\ \|\\ H-C-X\end{array}\right)$ to form ketones. Ketones are more reactive than acid halides. Therefore, as soon as a molecule of ketones is formed in the mixture, it reacts with a second molecule of G.R. After hydrolysis, the product is 3° alcohol, with two same alkyl groups that correspond to the alkyl portion of the G.R.

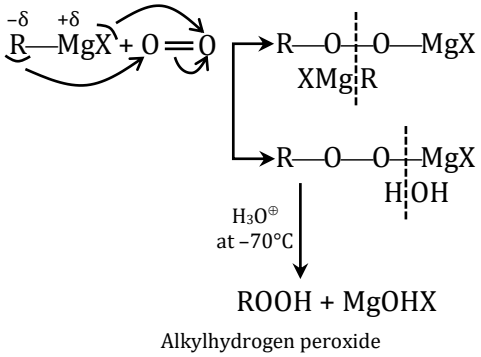


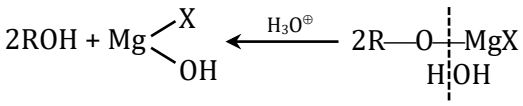
For example:



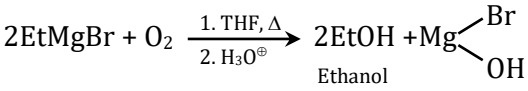
V. 1° Alcohol from O_2

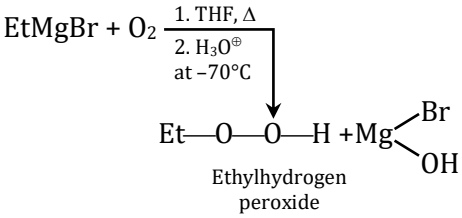
G.R. react with O_2 to give 1° alcohol or alkyl hydrogen peroxide.





For example:

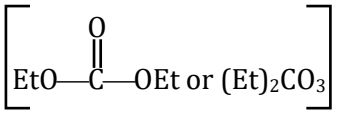
i. 

ii. 

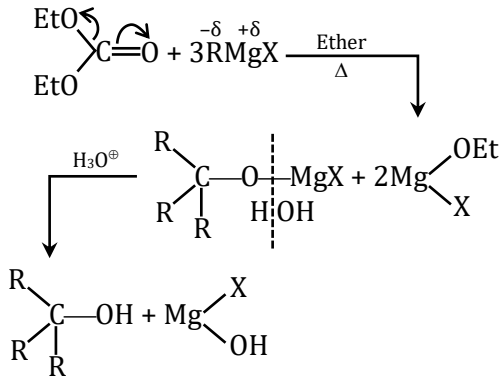
VI. Diethyl carbonate method :

Preparation of 3° alcohol containing three identical alkyl groups:

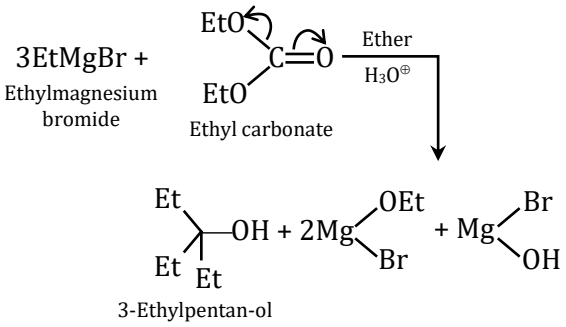
These may be prepared by the reaction between 3 mol of G.R. with 1 mol of diethyl carbonate.



Three R values are obtained from the following example:



For example:



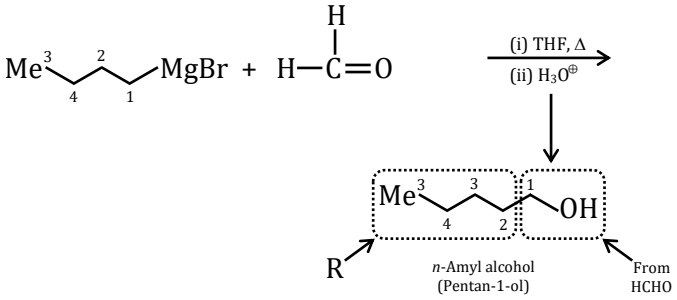
PLANNING THE SYNTESIS OF ALCOHOLS FROM GRIGNARD REAGENTS

To choose the correct G.R. and correct aldehyde, ketone, ester, anhydride, or epoxide, one has to examine the alcohol containing different groups attached to the C atom bearing the (–OH) group.

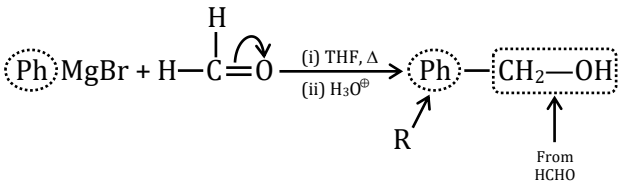
a. Synthesis of 1° alcohol:

i. Suppose we want to prepare *n*-amylalcohol (pentan-1-ol). 1° ROH is prepared from HCHO and RMgX. One C atom is obtained from HCHO; therefore, out of the total five C atoms in alcohol, alkyl group (R–) in the G.R. should have four C atoms.

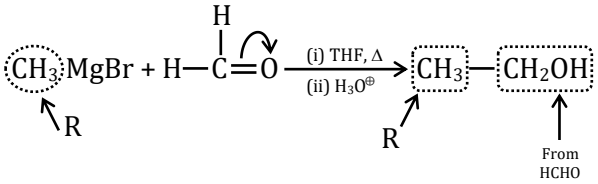
The value of R in G.R. is one C atom less than the total C atoms in alcohol. G.R. should be C_4H_9MgBr.

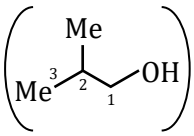


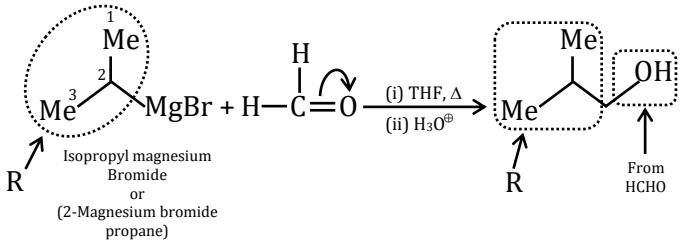
ii. Benzyl alcohol ($PhCH_2OH$) from G.R.



iii. Methyl carbinol (ethanol, CH_2CH_2OH) from G.R.

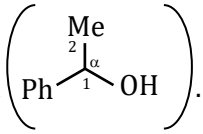


iv. 2-Methyl propanol  from G.R.



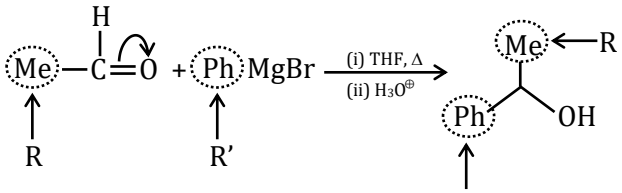
b. Synthesis of 2° alcohol:

i. Suppose we want to prepare 1-phenyl ethanol or

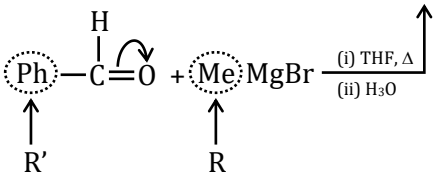
α-phenyl ethanol  .

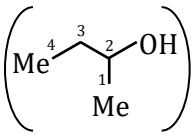
2° alcohols are prepared by the reaction of aldehyde (R—CHO) and R'MgX. The values of R and R' in the compounds are Ph and Me or Me and Ph.

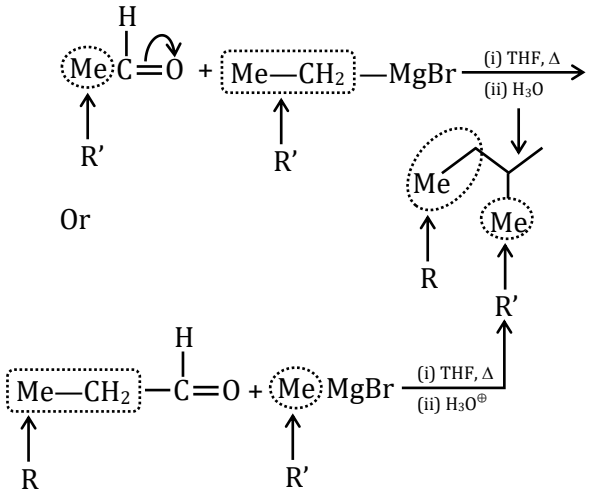
First method:



Second method:

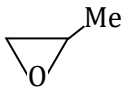


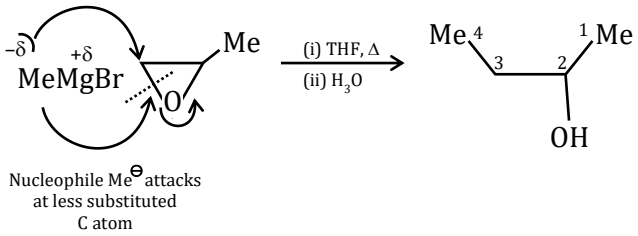
ii. Butan-2-ol  from G.R.



iii. Butan-2-ol from G.R. and oxirane:

R and R' in butan-2-ol are Me and Et.

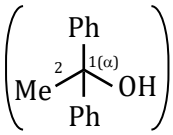
The G.R. can only be MeMgBr, oxirane can be 



iv. Butan-2-ol cannot be prepared by formic ester or formic anhydride or formyl chloride method, since the two R groups are different.

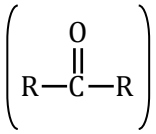
c. Synthesis of 3° alcohol:

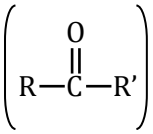
Suppose 1,1-diphenyl ethanol or α, α-diphenyl ethanol



has to be prepared.

3° alcohols are prepared by the reaction of ketone with

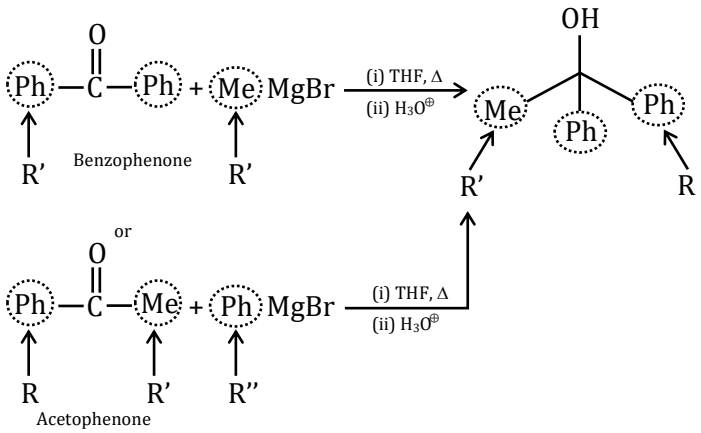


or


with R'' MgX.

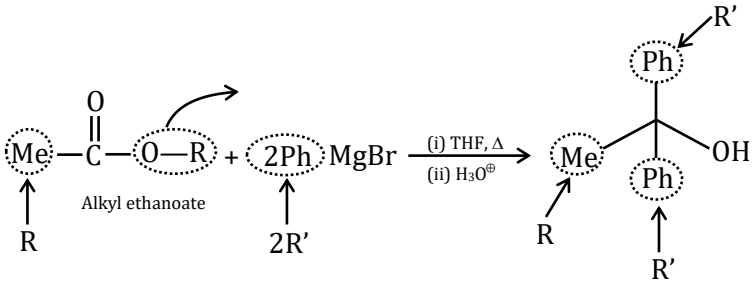
The values of R and R' in the compounds are Me and Ph.

First method:

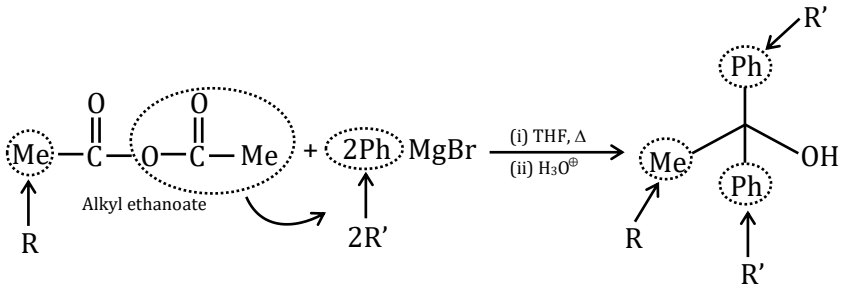


Second method : Using the ester, acid anhydride, and acid chloride methods, only 3° alcohols can be prepared which have at least two same alkyl groups, since 2 mol of RMgX has to be used and the G.R. should be PhMgBr.

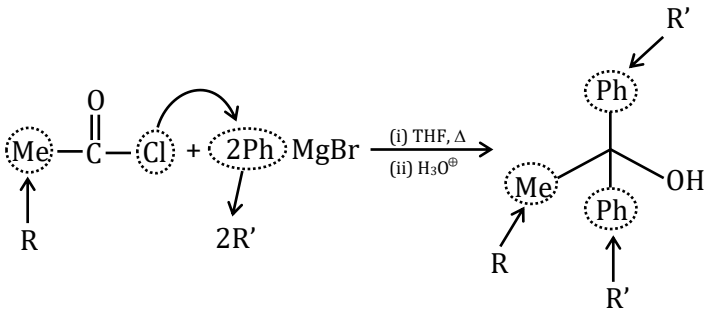
Ester method : Ester should be $Me-\overset{\overset{O}{\|}}{C}-O-R$ (here, in the ester R can be any group, since the formation of 3° alcohol does not depend on the value of this R group, because it has to be removed).



Acid anhydride method : Acid anhydride should be acetic anhydride $\left(Me-\overset{\overset{O}{\|}}{C}-O-\overset{\overset{O}{\|}}{C}-Me\right)$ and G.R. should be PhMgBr.



Acid chloride method: Acid chloride should be acetyl chloride $\left(Me-\overset{\overset{O}{\|}}{C}-Cl\right)$ (ethanol or acetyl chloride) and G.R. should be PhMgBr.



Note: In ester, acid anhydride, and acid halide, cyanide and amide methods, if R is Me, then the name of ester, acid halide, or acid anhydride should be with one more C atom; for example, if R is Me, name of the ester is alkyl ethanoate; if R is Et, name of the ester is alkyl propanoate. Similarly, for acid anhydride and acid halide methods,

	Acid anhydride	Acid halide
If R is Me ⟶	Ethanoic anhydride	Ethanoyl halide
If R is Et ⟶	Propanoic anhydride	Propanoyl halide

Illustration 1:

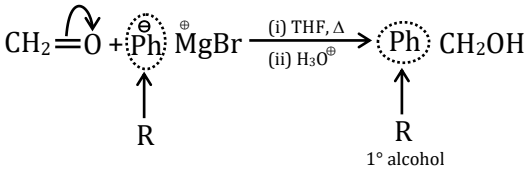
Synthesise the following:

a. Benzyl alcohol from G.R.

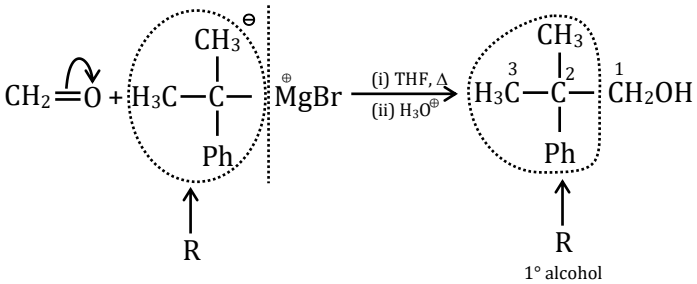
b. 2-Methyl-2-phenyl propanol from G.R.

Solution:

a.

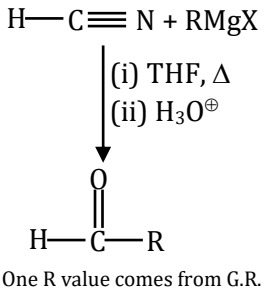
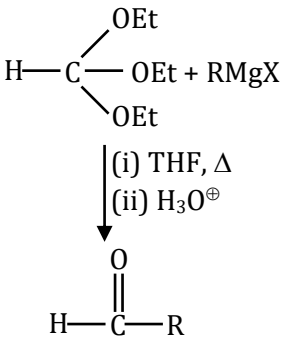
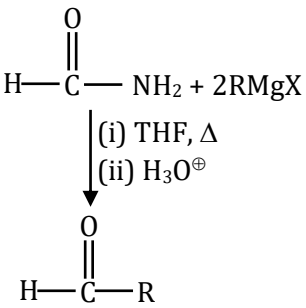
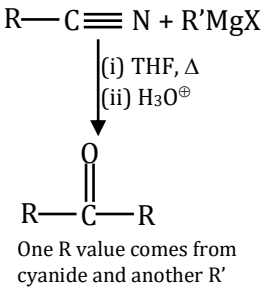
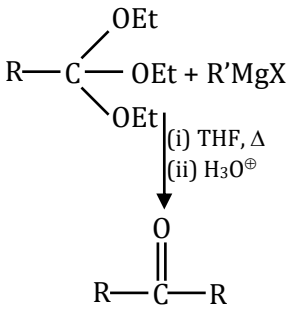
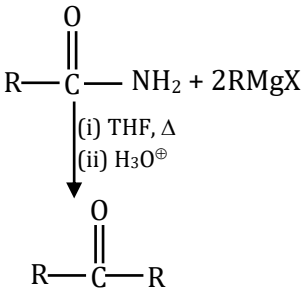


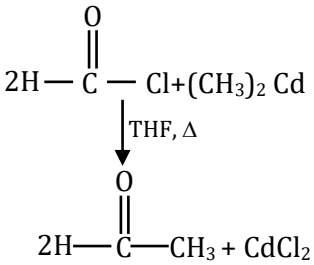
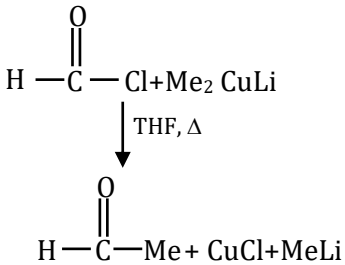
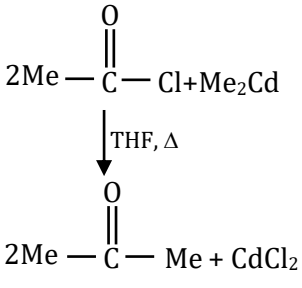
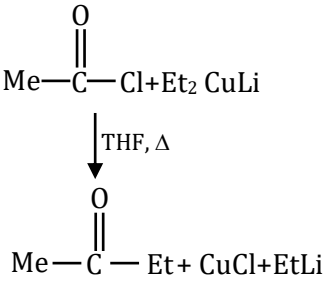
b.



PREPARATION OF ALDEHYDES AND KETONES

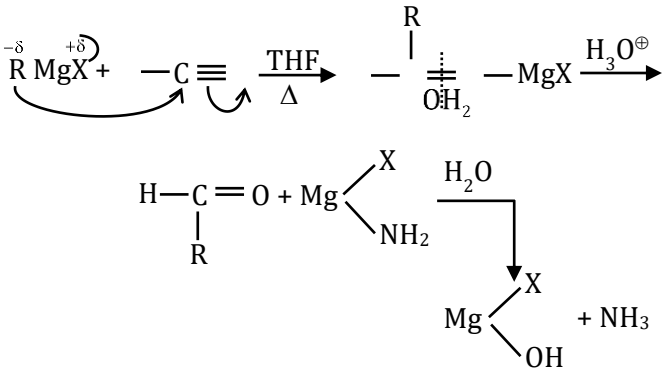
Table :- Summary of preparation of aldehydes and ketones

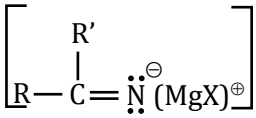
	Cyanide method (I)	Alkyl ortho ester method (II)	Amide method (III)
Aldehyde	 One R value comes from G.R.	 One R value comes from G.R.	 One R value comes from G.R.
Ketone	 One R value comes from cyanide and another R' value comes from G.R.	 One R value comes from ortho ester and another R' value comes from G.R.	 One R value comes from amide and another R' value comes from G.R.

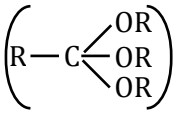
	Dialkyl Cadmium with acid halide (IV)	With dialkyl lithium cooperate with halide (V)
Aldehyde		
Ketone		

CYANIDE METHOD

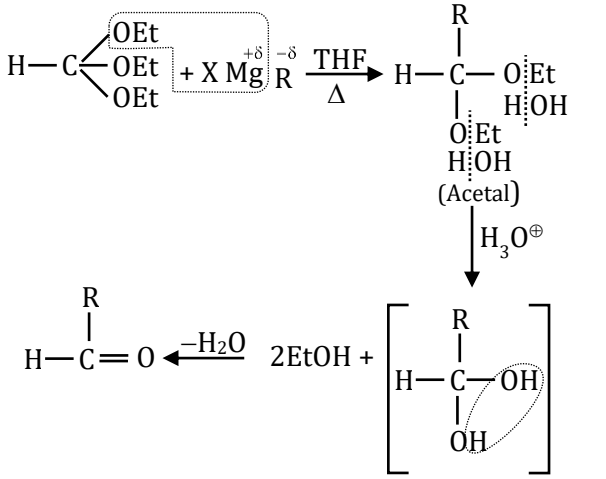
Reaction of G.R. with $H-C\equiv N$ gives aldehydes and with $R-C\equiv N$ gives ketones.

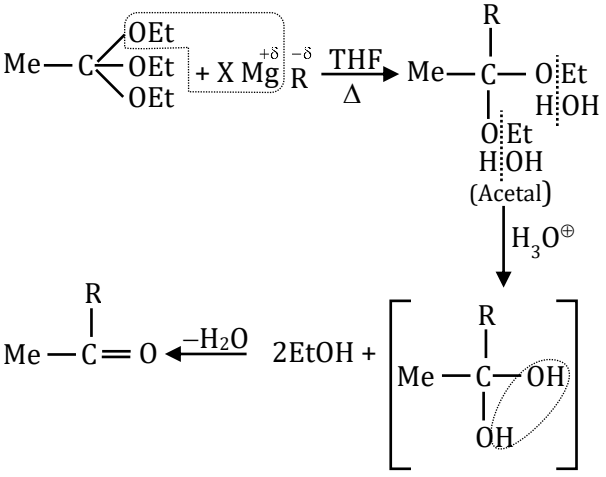


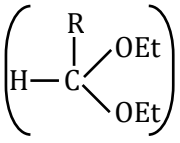
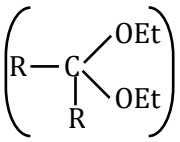
Note : A second equivalent of R'MgX does not react because the intermediate imine salt  bears a negative charge. So 3° alcohols are not formed in this method.

ALKYL ORTHO ESTER :  **METHOD**

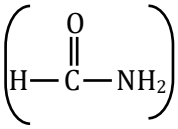
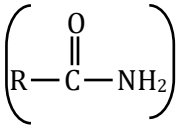
A better yield is obtained if RMgX reacts with ethylorthoformate to give ketone.



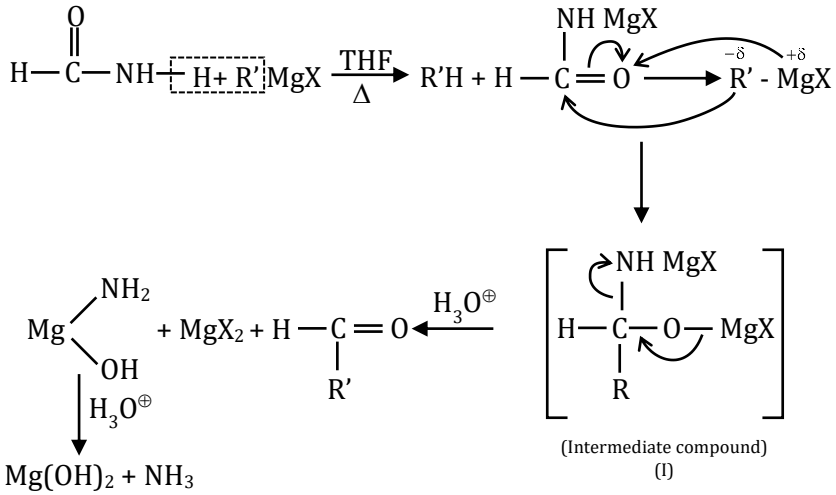


Note : In this reaction, $R^{\ominus}$ displaces $EtO^{\ominus}$, giving  or  (Acetal) which is unreactive with RMgX. Hence 2° alcohol is not formed.

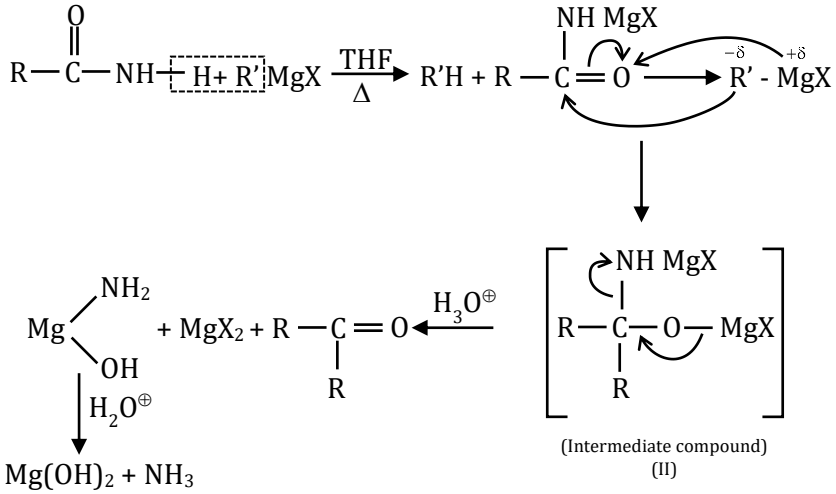
AMIDE METHOD :

Reaction of RMgX with methanamide or formamide  gives aldehyde, while other amides  ketones are obtained.

a.

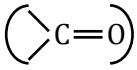


b.



Note : Aldehydes and ketones do not react further with G.R. to give 2° or 3° alcohols, because intermediate compound (I or II) is stable and is unreactive with G.R.

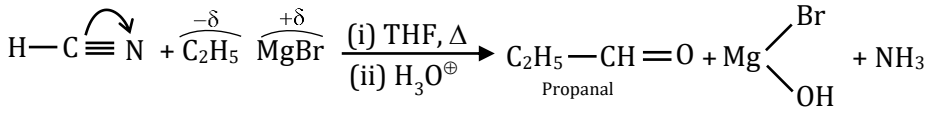
PLANNING THE SYNTHESIS OF ALDEHYDES AND KETONES FROM G.R.

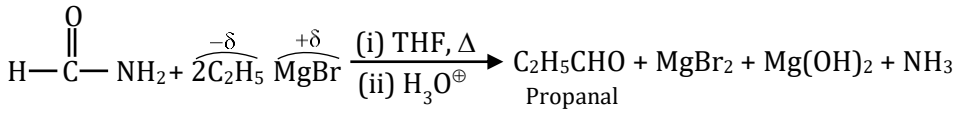
The choice of correct G.R. and correct cyanide, ortho formate, or amide is done by examining the aldehyde or ketone containing different groups attached to the carbonyl  group.

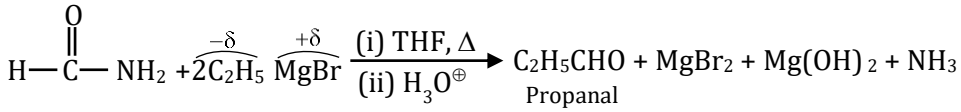
SYNTHESIS OF ALDEHYDES

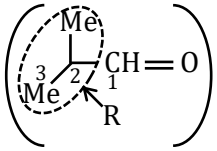
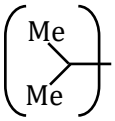
Suppose we want to prepare propanal (C_2H_5CHO). Aldehydes are prepared by cyanide, alkyl ortho ester, or amide method. In all these methods, the (–CHO) group is obtained from HCN, $HC(OEt)_3$, $HCONH_2$, and the alkyl group is obtained from G.R. The value of R in G.R. is one C atom less than the total number of C atoms in the aldehyde.

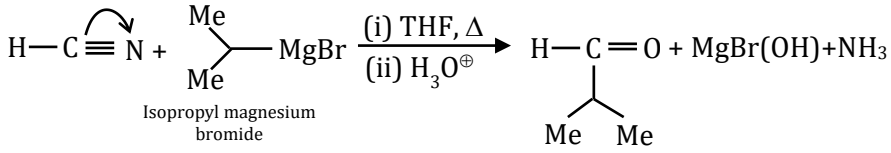
So, for the preparation of propanal (C_2H_5 – CHO), the value of R in G.R. is C_2H_5–.

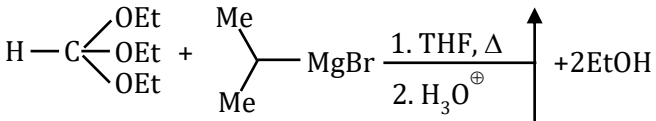
i. 

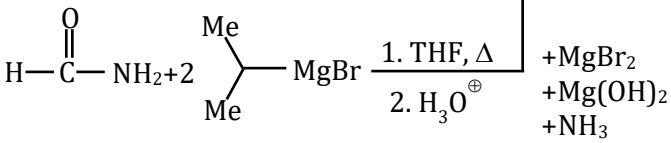
ii. 

iii. 

iv. 2-Methyl propanal  from G.R. The value of R in G.R. is  (isopropyl group)



v. 

vi. 

SYNTHESIS OF KETONES

Ketones ae prepared by the cyanide or amide method. Two R and R' group in ketone $R-\overset{O}{\overset{\|}{C}}-R'$ are obtained : one R from G.R. and one R' from cyanide or amide. The value of R' in cyanide or amide is one C atom less than total number of C atoms in the cyanide or amide.

i. Synthesis of acetophenone $Ph-\overset{O}{\overset{\|}{C}}-CH_3$ (R = Ph, R' = CH_3)

ii. $\overset{-\delta}{Ph}\ \overset{+\delta}{MgBr} + CH_3-C\equiv N$
Phenyl magnesium bromide; Ethanenitrile or Methyl cyanide

$CH_3-MgBr + Ph-C\equiv N$
Methyl magnesium bromide

iii. $Ph\ MgBr + 2CH_3-\overset{O}{\overset{\|}{C}}-NH_2$
Ethanamide or Acetamide

iv. $CH_3-MgBr + 2Ph-\overset{O}{\overset{\|}{C}}-NH_2$
Benzamide

$\xrightarrow[2.\ H_3O^{\oplus}]{1.\ THF,}$

$CH_3-\overset{O}{\overset{\|}{C}}-Ph + MgBr(OH) + NH_3$

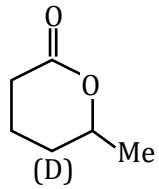
$CH_3-\overset{O}{\overset{\|}{C}}-Ph + MgBr(OH) + NH_3$

$CH_3-\overset{O}{\overset{\|}{C}}-Ph + MgBr_2 + Mg(OH)_2 + NH_3$

$CH_3-\overset{O}{\overset{\|}{C}}-Ph + MgBr_2 + Mg(OH)_2 + NH_3$

Illustration 2:

a. $2MeMgBr + CdCl_2 \rightarrow (A) \xrightarrow{2\ Ph-\overset{O}{\overset{\|}{C}}-Cl} (B) + (C)$

b.  (D) $+\ MeMgBr$ (E) $\xrightarrow[2.\ H_3O^{\oplus}]{1.\ THF,}$ (F)

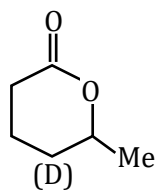
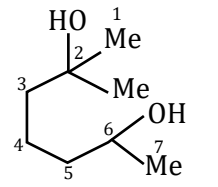
Solution:

a. (A) $\Rightarrow Me_2Cd$

$2\ Ph-\overset{O}{\overset{\|}{C}}-Cl + Me_2Cd \longrightarrow 2\ Ph-\overset{O}{\overset{\|}{C}}-Me + CdCl_2$

Benzoyl chloride; Dimethyl cadmium (A); (B) Acetophenone; (C) Cadmium chloride

b. (D) is a cyclic ester, called lactone. The ester reacts with 2 mol of G.R. to give 3° alcohol. (Two R group come from the G.R.)

 (D) $+\ 2Me\ Mg\ Br$ (E) $\xrightarrow[2.\ H_3O^{\oplus}]{1.\ THF,}$ 

R

2-Methylheptan-2, 6-diol (F)