Chem Factsheet

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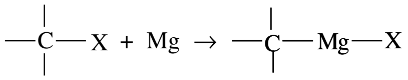
Using Grignard Reagents in Organic Synthesis

What is a 'Grignard Reagent'

A compound formed when a magnesium atom is inserted between the carbon and the halogen atom (X) in a halogeno-compound dissolved in anhydrous ether, CH_3CH_3-O-CH_2CH_3.



$$-\overset{|}{\underset{|}{C}}-X + Mg \rightarrow -\overset{|}{\underset{|}{C}}-Mg-X$$

How is this done?

Excess magnesium turnings are reacted with the halogeno-compound in sodium-dried ether. (It is important to stress **anhydrous conditions**- the Grignard Reagent rapidly reacts with water).

Note: Some of the answer points in mark schemes are not quite realistic, especially where an electrical heater is used ! The mixture is made under reflux and the reality is that the reaction is so exothermic once started that one has a beaker of iced water nearby just in case things get out of hand!

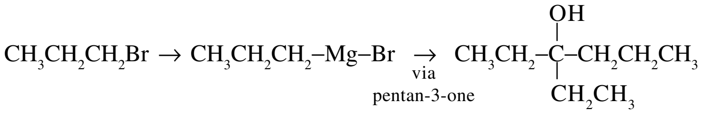
A crystal of iodine is added to activate the metal surface and the flask is warmed with hand heat until the rapid reaction starts. A **water bath** is used to give gentle reflux for 20+ minutes according to most sources but this is superfluous in real terms as the majority of the organic magnesium halide is formed prior to this point.

Why are they so important?

1. A point that is not often clear in texts is that carbon chains of any size and shape can be 'engineered'.

   e.g. To create a tertiary structure

1-bromopropane → Grignard → 3-ethylhexan-3-ol



$$CH_3CH_2CH_2Br \rightarrow CH_3CH_2CH_2{-}Mg{-}Br \xrightarrow[\text{via pentan-3-one}]{} CH_3CH_2{-}\overset{OH}{\underset{CH_2CH_3}{C}}{-}CH_2CH_2CH_3$$

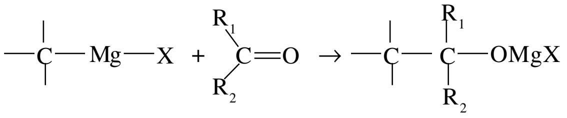
2. Extremely good yields (90%+) of products and high purities are possible. This is because (a) the by-products are inorganic and easily separated (b) there is no excess organic reactant and (c) the solvent is very volatile and easily removed.

Note: As mentioned earlier, Grignard Reagents are readily hydrolysed by traces of moisture and so are used **'in situ'** i.e. prepared and then reacted in the same apparatus.

How do they react?

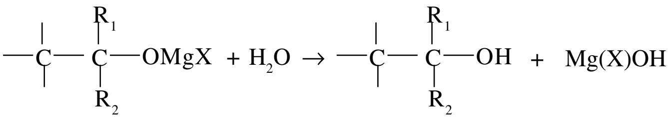
The essential point is that the carbon stem of the Grignard acts as a **nucleophile** to an electron deficient centre in a second reagent. This is usually a carbon atom *doubly bonded* to an electronegative oxygen atom (e.g. in an aldehyde, a ketone or carbon dioxide).

In effect, the Grignard completes a **nucleophilic addition** across the C=O double bond, the pi bond of which splits heterolytically, to form an intermediate magnesium complex.



$$-\overset{|}{\underset{|}{C}}-Mg-X + \overset{R_1}{\underset{R_2}{C}}=O \rightarrow -\overset{|}{\underset{|}{C}}-\overset{R_1}{\underset{R_2}{C}}-OMgX$$

This is then hydrolysed with **dilute acid** to form an OH group and a mixture of magnesium halide/hydroxide, Mg(X)OH. The acid catalyses the hydrolysis and converts the Mg(X))H to soluble magnesium salts.



$$-\overset{|}{\underset{|}{C}}-\overset{R_1}{\underset{R_2}{C}}-OMgX + H_2O \rightarrow -\overset{|}{\underset{|}{C}}-\overset{R_1}{\underset{R_2}{C}}-OH + Mg(X)OH$$

then $Mg(X)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + X^-(aq)$

Note : Nucleophilic addition to **epoxyethane** is also possible and useful. See later.

Predicting Reactants from Desired Products

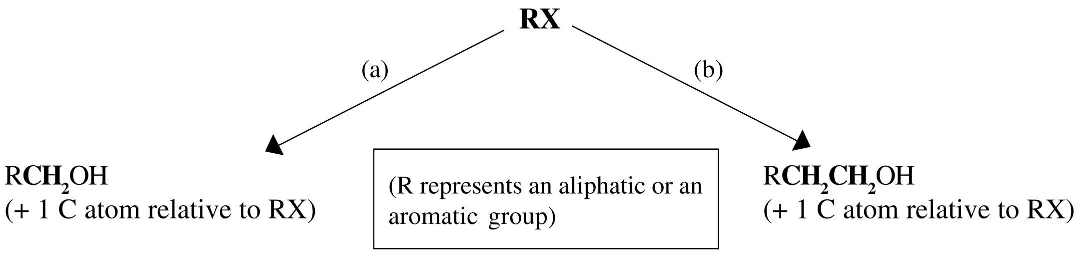
Used appropriately, Grignards allow the following as possible products :

Primary / secondary / tertiary alcohols and carboxylic acids

Most of the questions you will encounter involve stating *which reactants you would need* to prepare a given product. You need to consider the essential molecular transformation and *work backwards*.

1. To synthesise a primary alcohol, (RCH_2OH)

You have two choices, either adding one or two CH_2 groups – see routes (a) and (b) in the following diagram. If the desired product has “n” carbons, you must choose a starting molecule with “n-1” carbons to use (a) but “n-2” carbons to use (b)



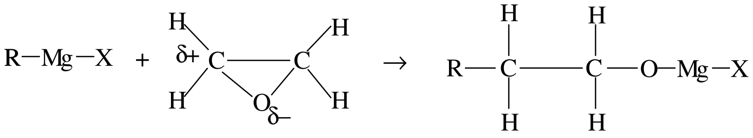
Route (a):
Use **METHANAL** (HCHO) to provide the C=O and the single C.

In general: (1) $\mathrm{R{-}Br + Mg \rightarrow R{-}Mg{-}Br}$
then (2) $\mathrm{R{-}Mg{-}Br + \mathbf{HCHO} \rightarrow R{-}\mathbf{CH_2}{-}O{-}MgBr}$
then (3) $\mathrm{R{-}\mathbf{CH_2}{-}OMgBr + H_2O \rightarrow R{-}\mathbf{CH_2}{-}OH + Mg(Br)OH}$
then (4) $\mathrm{Mg(Br)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + Br^-(aq)}$

eg Converting 1-bromo**prop**ane to **but**an-1-ol

(1) $\mathrm{CH_3CH_2CH_2{-}Br + Mg \rightarrow CH_3CH_2CH_2{-}Mg{-}Br}$
then (2) $\mathrm{CH_3CH_2CH_2{-}Mg{-}Br + \mathbf{HCHO} \rightarrow CH_3CH_2CH_2{-}\mathbf{CH_2}{-}O{-}MgBr}$
then (3) $\mathrm{CH_3CH_2CH_2{-}\mathbf{CH_2}{-}OMgBr + H_2O \rightarrow CH_3CH_2CH_2{-}\mathbf{CH_2}{-}OH + Mg(Br)OH}$
then (4) $\mathrm{Mg(Br)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + Br^-(aq)}$

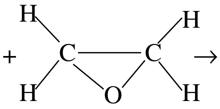
Route (b):
Use **EPOXYETHANE**



Note : epoxyethane has a strained 3-member ring. The nucleophilic Grignard attacks the δ+ C causing the C-O bond to break heterolytically. This is analogous to the breaking of the pi bond of methanal in route (a).

eg 1-bromo**prop**ane → **pentan**-1-ol

(1) $\mathrm{CH_3CH_2CH_2{-}Br + Mg \rightarrow CH_3CH_2CH_2{-}Mg{-}Br}$

then (2) $\mathrm{CH_3CH_2CH_2{-}Mg{-}Br}$ +  $\mathrm{\rightarrow CH_3CH_2CH_2{-}\mathbf{CH_2}{-}\,\mathbf{CH_2}{-}O{-}MgBr}$

then (3) $\mathrm{CH_3CH_2CH_2{-}\mathbf{CH_2}{-}\mathbf{CH_2}{-}OMgBr + H_2O \rightarrow CH_3CH_2CH_2{-}\mathbf{CH_2}{-}\,\mathbf{CH_2}{-}OH + Mg(Br)OH}$

then (4) $\mathrm{Mg(Br)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + Br^-(aq)}$

2. To synthesise a secondary alcohol $R_1CH(OH)R_2$

Use **AN APPROPRIATE ALDEHYDE** (R_2CHO) to provide the C=O and the extra C atoms, R_2.

In general: (1) R_1-Br + Mg → R_1-Mg-Br
then (2) R_1-Mg-Br + $\mathbf{R_2CHO}$ → R_1-$\mathbf{CH}$(OMgBr)-$\mathbf{R_2}$
then (3) R_1-$\mathbf{CH}$(OMgBr)-$\mathbf{R_2}$ + H_2O → R_1-$\mathbf{CH}$(OH)-$\mathbf{R_2}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

e.g. If we want **hexan**-3-ol [$\mathbf{CH_3CH_2}$CH(OH)$\mathbf{CH_2CH_2CH_3}$; a 6 C alcohol with a 2C and a 3C unit on either side of the CH(OH) functional group] we could use :

(a) Bromoethane (2C) to make the Grignard which is then reacted with butanal (4C)

or (b) 1-Bromopropane (3C) to make the Grignard which is then reacted with propanal (3C).

By route (a)

(1) $\mathbf{CH_3CH_2}$-Br + Mg → $\mathbf{CH_3CH_2}$-Mg-Br
then (2) $\mathbf{CH_3CH_2}$-Mg-Br + $\mathbf{CH_3CH_2CH_2}$CHO → $\mathbf{CH_3CH_2}$-CH(OMgBr)-$\mathbf{CH_2CH_2CH_3}$
then (3) $\mathbf{CH_3CH_2}$-CH(OMgBr)-$\mathbf{CH_2CH_2CH_3}$ + H_2O → $\mathbf{CH_3CH_2}$-CH(OH)-$\mathbf{CH_2CH_2CH_3}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

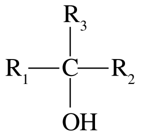
By route (b)

(1) $\mathbf{CH_3CH_2CH_2}$-Br + Mg → $\mathbf{CH_3CH_2CH_2}$-Mg-Br
then (2) $\mathbf{CH_3CH_2CH_2}$-Mg-Br + $\mathbf{CH_3CH_2}$CHO → $\mathbf{CH_3CH_2CH_2}$-CH(OMgBr)-$\mathbf{CH_2CH_3}$
then (3) $\mathbf{CH_3CH_2CH_2}$-CH(OMgBr)-$\mathbf{CH_2CH_3}$ + H_2O → $\mathbf{CH_3CH_2CH_2}$-CH(OH)-$\mathbf{CH_2CH_3}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

Note : Be careful! Choosing 1-bromobutane (4C) and ethanal (2C) gives hexan-2-ol!
(1) $\mathbf{CH_3CH_2CH_2CH_2}$-Br + Mg → $\mathbf{CH_3CH_2CH_2CH_2}$-Mg-Br
then (2) $\mathbf{CH_3CH_2CH_2CH_2}$-Mg-Br + $\mathbf{CH_3}$CHO → $\mathbf{CH_3CH_2CH_2CH_2}$-CH(OMgBr)-$\mathbf{CH_3}$
then (3) $\mathbf{CH_3CH_2CH_2CH_2}$-CH(OMgBr)-$\mathbf{CH_3}$ + H_2O → $\mathbf{CH_3CH_2CH_2CH_2}$-CH(OH)-$\mathbf{CH_3}$ + Mg(Br)OH

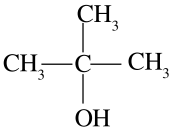
3. To synthesise a tertiary alcohol

The general formula of a tertiary alcohol is



$$R_1-\overset{\displaystyle R_3}{\underset{\displaystyle OH}{C}}-R_2$$

Hence, use **AN APPROPRIATE KETONE** (R_1COR_2) to provide the C=O and the extra C atoms, R_1 and R_2.
So, if we are asked to synthesise 2-methylpropan-2-ol,

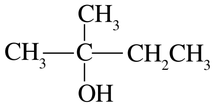


$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-CH_3$$

we need to choose bromomethane ($R_3 = CH_3$) to make the Grignard which is then reacted with propanone ($R_1 = R_2 = CH_3$).

(1) $\mathbf{CH_3}$-Br + Mg → $\mathbf{CH_3}$-Mg-Br
then (2) $\mathbf{CH_3}$-Mg-Br + $\mathbf{CH_3COCH_3}$ → $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_3}$
then (3) $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_3}$ + H_2O → $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OH)-$\mathbf{CH_3}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

However, if we are asked to synthesise 2-methylbutan-2-ol



$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle OH}{C}}-CH_2CH_3$$

we could :

(a) choose **bromoethane** ($R_2 = CH_2CH_3$) to make the Grignard, followed by reaction with **propanone** ($R_1 = R_3 = CH_3$)

or (b) choose **bromomethane** ($R_2 = CH_3$)to make the Grignard, followed by reaction with **butanone** ($R_1 = CH_3$ and $R_3 = CH_2CH_3$).

By route (a)

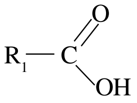
(1) $\mathbf{CH_3CH_2}$-Br + Mg → $\mathbf{CH_3CH_2}$-Mg-Br
then (2) $\mathbf{CH_3CH_2}$-Mg-Br + $\mathbf{CH_3COCH_3}$ → $\mathbf{CH_3CH_2}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_3}$
then (3) $\mathbf{CH_3CH_2}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_3}$ + H_2O → $\mathbf{CH_3CH_2}$-C($\mathbf{CH_3}$)(OH)-$\mathbf{CH_3}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

By route (b)

(1) $\mathbf{CH_3}$-Br + Mg → $\mathbf{CH_3}$-Mg-Br
then (2) $\mathbf{CH_3}$-Mg-Br + $\mathbf{CH_3CH_2COCH_3}$ → $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_2CH_3}$
then (3) $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OMgBr)-$\mathbf{CH_2CH_3}$ + H_2O → $\mathbf{CH_3}$-C($\mathbf{CH_3}$)(OH)-$\mathbf{CH_2CH_3}$ + Mg(Br)OH
then (4) Mg(Br)OH + H^+ → Mg^{2+}(aq) + H_2O(l) + Br^-(aq)

4. To synthesise a carboxylic acid

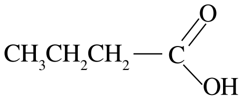
The general formula of a carboxylic acid is



$R_1-C(=O)OH$

Hence, use **CARBON DIOXIDE** (O=C=O) to provide the C=O and the extra C atom.

So, if we are asked to synthesise butanoic,



$CH_3CH_2CH_2-C(=O)OH$

we need to choose bromopropane ($R_1 = CH_3CH_2CH_2$) to make the Grignard which is then reacted with carbon dioxide.

> Note: the carbon dioxide is NOT used in gaseous form but as a ***solid*** ("Dri-ice").

(1) $\mathbf{CH_3CH_2CH_2}\text{-Br} + Mg \rightarrow \mathbf{CH_3CH_2CH_2}\text{-Mg-Br}$
then (2) $\mathbf{CH_3CH_2CH_2}\text{-Mg-Br} + \boldsymbol{O{=}C}{=}O \rightarrow \mathbf{CH_3CH_2CH_2}\boldsymbol{CO}(OMgBr)$
then (3) $\mathbf{CH_3CH_2CH_2}\boldsymbol{CO}(OMgBr) + H_2O \rightarrow \mathbf{CH_3CH_2CH_2}\boldsymbol{CO}OH + Mg(Br)OH$
then (4) $Mg(Br)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + Br^-(aq)$

> Note: This could be used to prepare the corresponding primary alcohol. The butanoic acid can be reduced to butan-1-ol using lithium aluminium hydride but methanal + the propyl Grignard reagent is the expected route, as seen earlier.

Additional Notes

1. The bromo-compound is used here because this is usually quoted in A Level questions. In practical terms this and the iodo-reactants are used because the magnesium complex is more difficult to form with the chloride due to the much higher bond energy of C-Cl.

2. Other epoxides can be used apart from epoxyethane to produce branched chain primary alcohols but this is beyond the parameters of A Level.

3. Grignard reagents react with water as follows: $RMgX + H_2O \rightarrow RH + Mg(OH)X$

   This is why the first two stages must be under **anhydrous conditions**. However, it does provide a means of replacing efficiently a halogen atom in a structure with hydrogen atom !

Practice Questions

Devise a **full** synthesis for each of the following molecules using an appropriate Grignard reagent

1. Benzoic acid (C_6H_5COOH)

2. 3-Ethylhexan-3-ol

3. Butan-2-ol

4. Heptan-1-ol

Answers

Note : step (d) of (1) is also applicable to (3) – (4).

1. (a) $\mathrm{C_6H_5\text{-}Br + Mg \rightarrow C_6H_5\text{-}Mg\text{-}Br}$
then (b) $\mathrm{C_6H_5\text{-}Mg\text{-}Br} + \mathit{O{=}C}\mathrm{{=}O} \rightarrow \mathrm{C_6H_5}\mathit{CO}\mathrm{(OMgBr)}$
then (c) $\mathrm{C_6H_5}\mathit{CO}\mathrm{(OMgBr) + H_2O \rightarrow C_6H_5}\mathit{CO}\mathrm{OH + Mg(Br)OH}$
then (d) $\mathrm{Mg(Br)OH + H^+ \rightarrow Mg^{2+}(aq) + H_2O(l) + Br^-(aq)}$

2. This is a tertiary alcohol. Hence,

(1) Use bromoethane and hexan-3-one or (2) 1-bromopropane and pentan-3-one

By route (1)
(a) $\mathrm{CH_3CH_2\text{-}Br + Mg \rightarrow CH_3CH_2\text{-}Mg\text{-}Br}$
then (b) $\mathrm{CH_3CH_2\text{-}Mg\text{-}Br + CH_3CH_2COCH_2CH_2CH_3 \rightarrow CH_3CH_2\text{-}C(CH_2CH_3)(OMgBr)\text{-}CH_2CH_2CH_3}$
then (c) $\mathrm{CH_3CH_2\text{-}C(CH_2CH_3)(OMgBr)\text{-}CH_2CH_2CH_3 + H_2O \rightarrow CH_3CH_2\text{-}C(CH_2CH_3)(OH)\text{-}CH_2CH_2CH_3 + Mg(Br)OH}$

By route (2)
(a) $\mathrm{CH_3CH_2CH_2\text{-}Br + Mg \rightarrow CH_3CH_2CH_2\text{-}Mg\text{-}Br}$
then (b) $\mathrm{CH_3CH_2CH_2\text{-}Mg\text{-}Br + CH_3CH_2COCH_2CH_3 \rightarrow CH_3CH_2CH_2\text{-}C(CH_2CH_3)(OMgBr)\text{-}CH_2CH_3}$
then (c) $\mathrm{CH_3CH_2CH_2\text{-}C(CH_2CH_3)(OMgBr)\text{-}CH_2CH_3 + H_2O \rightarrow CH_3CH_2CH_2\text{-}C(CH_2CH_3)(OH)\text{-}CH_2CH_3 + Mg(Br)OH}$

3. This is a secondary alcohol. Hence,

(1) Use bromomethane and propanal or (2) bromoethane and ethanal

By route (1)
(a) $\mathrm{CH_3\text{-}Br + Mg \rightarrow CH_3\text{-}Mg\text{-}Br}$
then (b) $\mathrm{CH_3\text{-}Mg\text{-}Br + CH_3CH_2CHO \rightarrow CH_3CH(OMgBr)\text{-}CH_2CH_3}$
then (c) $\mathrm{CH_3CH(OMgBr)\text{-}CH_2CH_3 + H_2O \rightarrow CH_3CH(OH)\text{-}CH_2CH_3 + Mg(Br)OH}$

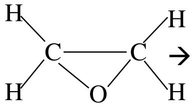
By route (2)
(a) $\mathrm{CH_3CH_2\text{-}Br + Mg \rightarrow CH_3CH_2\text{-}Mg\text{-}Br}$
then (b) $\mathrm{CH_3CH_2\text{-}Mg\text{-}Br + CH_3CHO \rightarrow CH_3CH_2\text{-}CH(OMgBr)\text{-}CH_3}$
then (c) $\mathrm{CH_3CH_2\text{-}CH(OMgBr)\text{-}CH_3 + H_2O \rightarrow CH_3CH_2\text{-}CH(OH)\text{-}CH_3 + Mg(Br)OH}$

4. This is a primary alcohol. Hence,

(1) Use 1- bromohexane and methanal or (2) 1-bromopentane and epoxyethane

By route (1)
(a) $\mathrm{CH_3CH_2CH_2CH_2CH_2CH_2\text{-}Br + Mg \rightarrow CH_3CH_2CH_2CH_2CH_2CH_2\text{-}Mg\text{-}Br}$
then (b) $\mathrm{CH_3CH_2CH_2CH_2CH_2CH_2\text{-}Mg\text{-}Br + HCHO \rightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH(OMgBr)\text{-}H}$
then (c) $\mathrm{CH_3CH_2CH_2CH_2CH_2CH_2CH(OMgBr)\text{-}H + H_2O \rightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH + Mg(Br)OH}$

By route (2)
(a) $\mathrm{CH_3CH_2CH_2CH_2CH_2\text{-}Br + Mg \rightarrow CH_3CH_2CH_2CH_2CH_2\text{-}Mg\text{-}Br}$

then (b) $\mathrm{CH_3CH_2CH_2CH_2CH_2\text{-}Mg\text{-}Br}$ +  → $\mathrm{CH_3CH_2CH_2CH_2CH_2\text{-}CH_2\text{-}CH_2\text{-}O\text{-}MgBr}$

then (c) $\mathrm{CH_3CH_2CH_2CH_2CH_2\text{-}CH_2\text{-}CH_2\text{-}OMgBr + H_2O \rightarrow CH_3CH_2\,CH_2CH_2CH_2\text{-}CH_2\text{-}CH_2\text{-}OH + Mg(Br)OH}$

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