Chemistry Olympiad

ROYAL SOCIETY OF CHEMISTRY

UK Chemistry Olympiad support resources: organic synthesis

Introduction

Synthesis of a target molecule such as a drug or pesticide is a common challenge for organic chemists. Once a molecule is identified as a suitable target, the job of the organic chemist is to work out the most efficient way to synthesise that molecule. This requires developing a sequence of steps that start with a relatively simple, and readily available molecule, and builds to the final target molecule using the fewest number of steps and the most efficient reactions along the way.

Carbonyl chemistry

The carbonyl group (C=O) is without doubt the most important functional group in organic chemistry. It can be found in a wide range of compound types some of which are shown in figure 1.

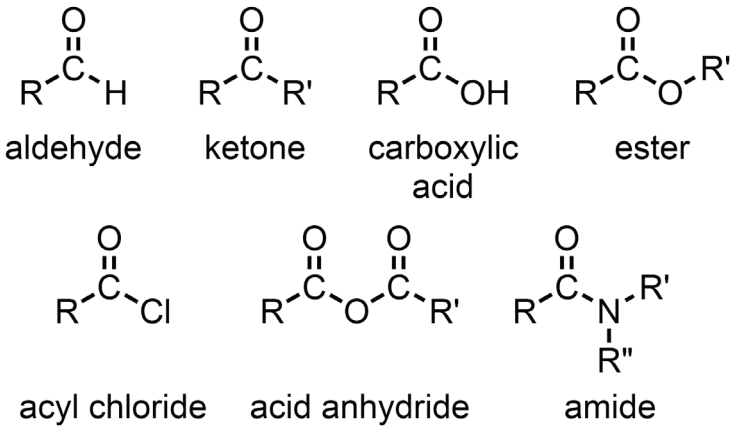


Figure 1 Molecules containing a carbonyl group (R, R' or R" = an alkyl or aryl group)

Molecules that contain a carbonyl group are excellent intermediates in a synthesis owing to the range of transformations they can undergo.

Oxygen is more electronegative than carbon. This leaves the carbon atom in a carbonyl group short of electron density and hence electrophilic. As such it can react with a range of nucleophiles resulting in the formation of a wide array of new compounds. Some of the most common transformations of aldehydes and ketones are shown in figure 2.

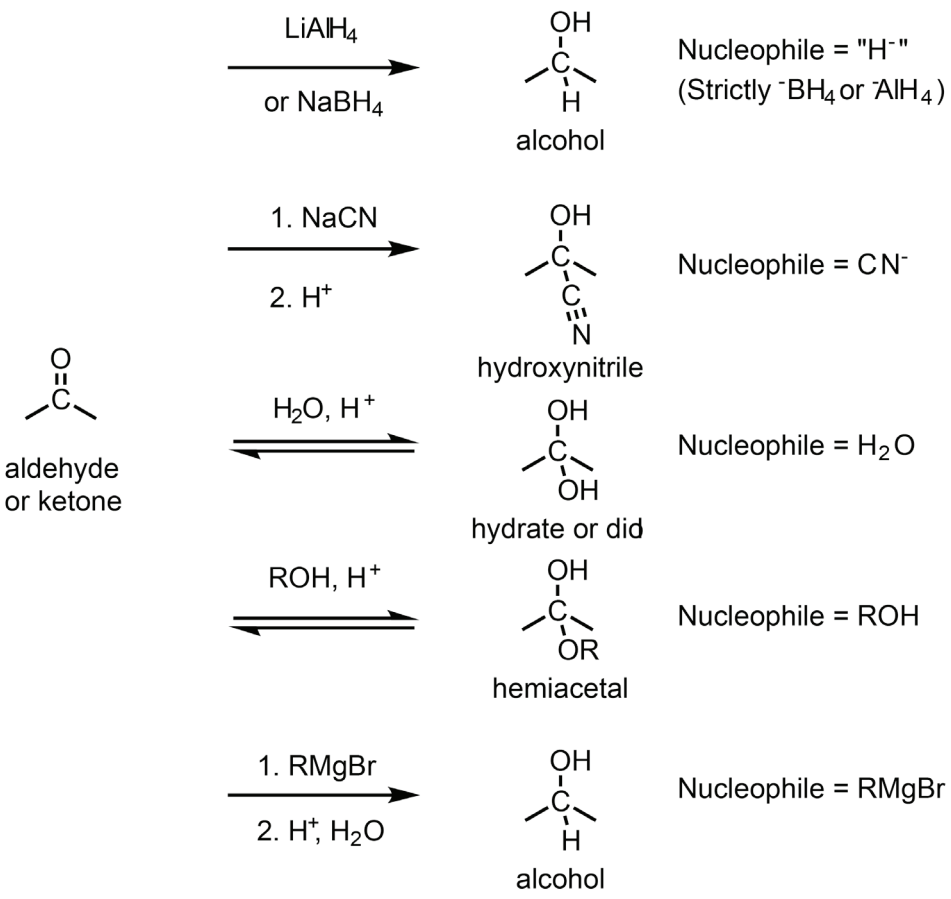


Figure 2 Transformations of aldehydes and ketones

Carboxylic acid derivatives are molecules that contain a carbonyl group with a heteroatom (an atom that is not carbon or hydrogen) attached to the carbon. Esters, acyl chlorides, acid anhydrides and amides are all examples of carboxylic acid derivatives.

Leaving groups are anions such as Cl^-, RO^- and $RCOO^-$ that can be expelled from a molecule taking their negative charge with them. Esters, acyl chloride and acid anhydrides contain a carbonyl group with one of these leaving groups attached to the carbonyl carbon atom. This means that once attack by a nucleophile has occurred the intermediate formed is unstable and collapses again by an elimination reaction. The best leaving group attached to the central carbon atom is eliminated and the C=O reformed. Figure 3 outlines the mechanism for such nucleophilic addition-elimination reactions.

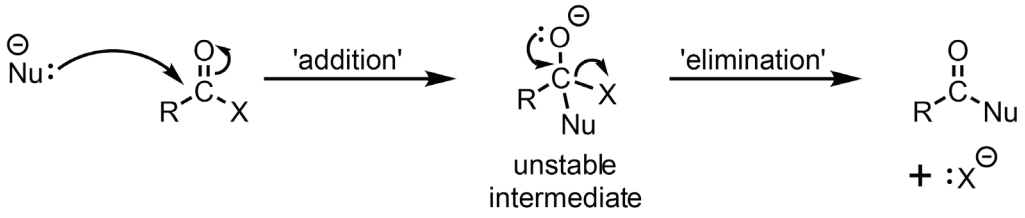


Figure 3 The mechanism of nucleophilic addition-elimination reactions where X represents a leaving group

As a result of this reaction, acyl chlorides in particular can be converted into a wide range of carboxylic acid derivatives.

Figure 4 gives an overview of some of the most common transformations involving carboxylic acid derivatives.

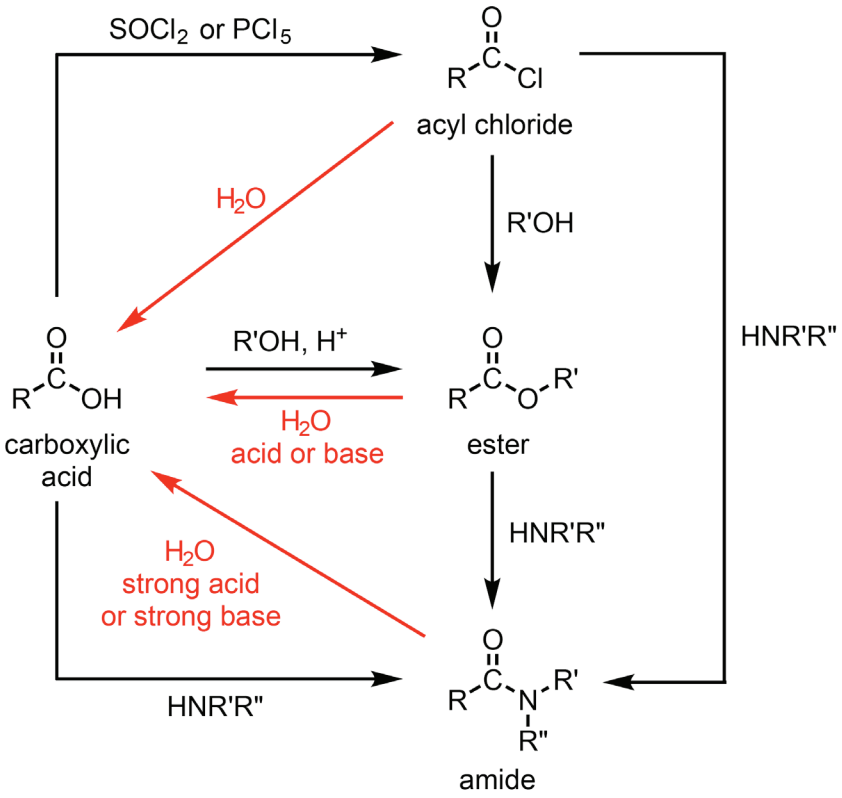


Figure 4 Interconversions of carboxylic acid derivatives

One important transformation from figure 4 to highlight is the conversion of a carboxylic acid into an acid chloride using $SOCl_2$ (or PCl_5). This is an extremely important transformation owing to the versatility of the acyl chloride produced. The same reagent can also be used to convert alcohols into chloroalkanes – another important functional group in an organic synthesis.

A final type of carbonyl compound of note is aromatic ketones. These can be formed from acyl chlorides via a Friedel-Crafts reaction using aluminium chloride as a catalyst.

In a Friedel-Crafts reaction, a hydrogen atom on a benzene ring in an aromatic compound is substituted for an acyl group to form an aromatic ketone as shown in figure 5.

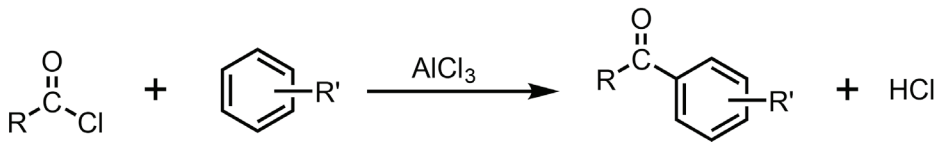
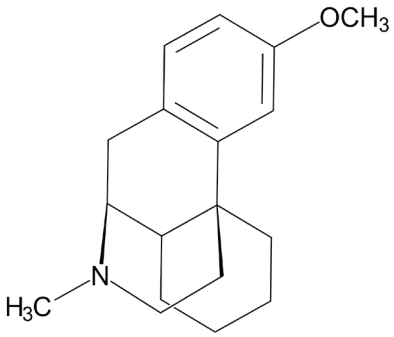


Figure 5 A Friedel-Crafts reaction between an acyl chloride and an aromatic compound. -R' represents an alkyl or aryl group attached at any position on the benzene ring

Worked example: UK Chemistry Olympiad 2018 paper 1 question 4

4. This question is about cough suppressants

In September 2017, the UK Prime Minister, Theresa May, had a bad cough during her speech at the Conservative Party Conference. The cough suppressant drug dextromethorphan, which is present in cough remedies such as Benylin®, could have helped her out. This question is about the synthesis of dextromethorphan. The synthesis involves the formation of some strong bonds and some stable carbocations.

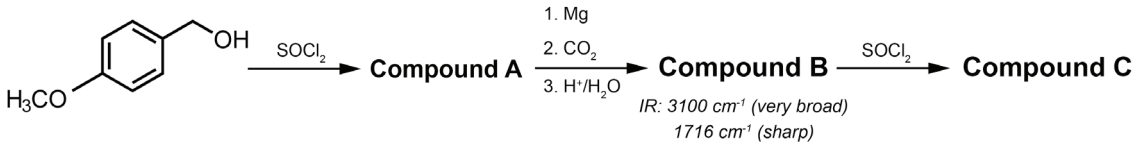


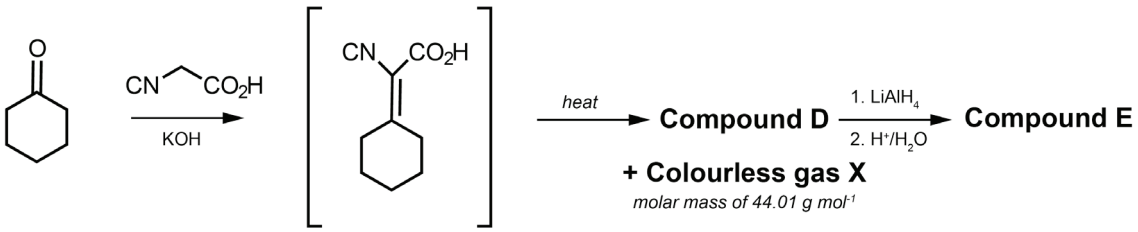
dextromethorphan

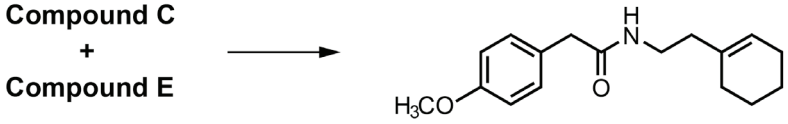
Dextromethorphan is often administered as the hydrobromide monohydrate salt.

The synthesis of dextromethorphan takes a number of steps. Please note that in the schemes describing the synthesis, by-products of the reactions are not always shown.

The synthesis of dextromethorphan begins with the synthesis of compound **F**.





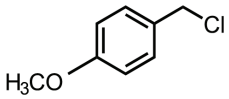


(c)

Draw the structures of compounds **A**, **B**, **C**, **D**, **E**, and gas **X**.

Answer to the worked example

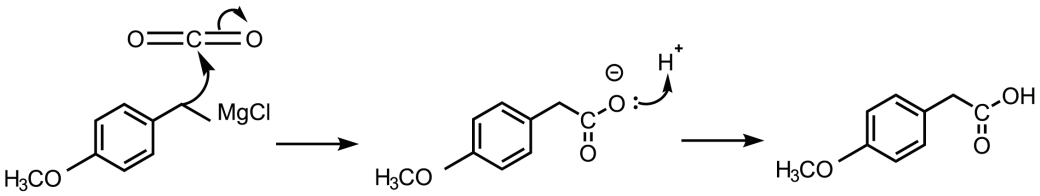
Compound **A** is formed from the reaction of the starting alcohol with $SOCl_2$. We know that alcohols are converted into chloroalkanes with $SOCl_2$. As there are no other functional groups in the molecule that could react with $SOCl_2$, compound **A** must therefore be:



Compound A

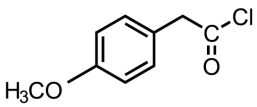
There are several clues to help us identify compound **B**. Firstly we can look at the infrared spectroscopy data provided. A broad absorption at 3100 cm^{-1} indicates the presence of an O-H (acid) bond. Together with the strong C=O absorption at 1716 cm^{-1}, this indicates that compound **B** contains a carboxylic acid group.

Secondly we can look at the reagents. When magnesium reacts with a halogenoalkane, an alkyl magnesium halide or Grignard reagent is formed. The carbon attached to the magnesium is nucleophilic and attacks the electrophilic carbon atom in carbon dioxide to form a carboxylic acid once protonated. You do not need to know this mechanism but it is interesting to see the similarity to the nucleophilic addition reactions of aldehydes and ketones with which you are familiar from your A-level studies. This gives compound **B** as the structure shown.



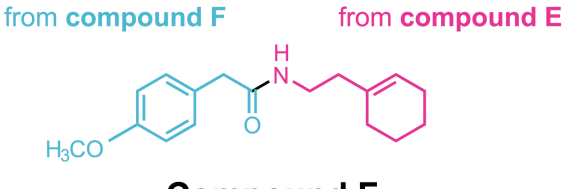
Compound B

Compound **B** contains a carboxylic acid group which is converted into an acyl chloride on reaction with $SOCl_2$ giving us compound **C**.



Compound C

Before moving on to look at compounds **D** and **E** it is worth noting that when attempting synthesis questions such as these that it is good practice to keep an eye on the final target molecule, in this case compound **F**. By looking at its structure we can see how compound **C** forms the left-hand half of the molecule and can envisage compound E as an amine that reacts with the acyl chloride in compound **C** to form the central amide bond.

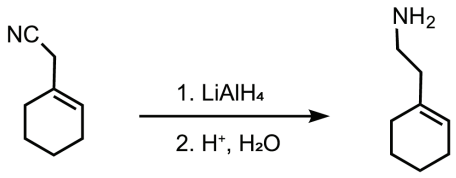


Compound F

To identify compound **D** and gas **X** we must first look at the clues given. Gas **X** has a molar mass of 44.01 g mol^{-1}. Of the most common gases only one has a molar mass of 44.01 g mol^{-1} which indicates that gas **X** is CO_2.

The intermediate carboxylic acid shown in the reaction scheme in the square brackets (in square brackets to indicate it is an intermediate and not isolated) must therefore lose CO_2 in a decarboxylation reaction to form compound **D**. We also know by looking ahead that compound **D** is reduced with $LiAlH_4$ to form an amine in compound **E**. As a nitrile group is reduced to an amine with LiAlH4 this suggests that the nitrile functional group is unaffected in the decarboxylation step and present in compound **D**. Keeping an eye on the final product it would also appear that the double bond moves into the ring during this step into the more stable position.

With this information to hand we can now conclude that compounds **D** and **E** have the structures shown below.



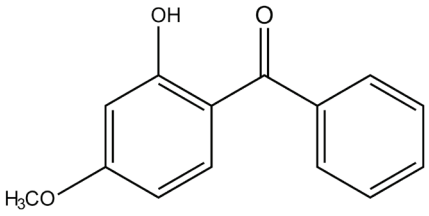
Compound D **Compound E**

TOP TIP A common error is to omit the carbon atom of the nitrile group when reducing a nitrile to form an amine. Avoid this by checking the number of carbon atoms in the reactant and product.

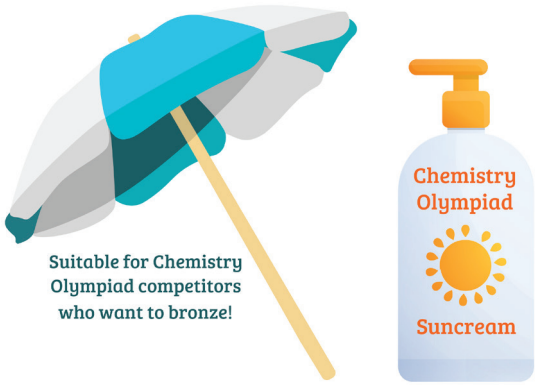
Now you have a go: RSC Chemistry Olympiad 2020 Round 1 Question 3

3. The question is about sun cream

On 1st January, the Pacific island of Palau imposed a ban on certain sun creams to protect its coral reefs. The ban restricts the use of ten products which are toxic to marine life and are linked to the bleaching of coral. Scientists are particularly concerned with two UV light-absorbing chemicals: oxybenzone and octinoxate.

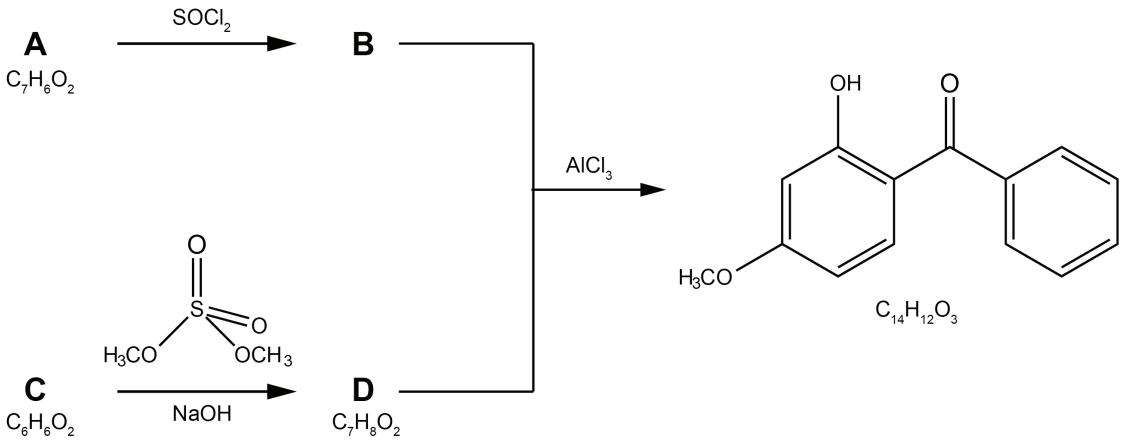


oxybenzone



HINT Remember that $AlCl_3$ is a catalyst in the Friedel-Crafts acylation of aromatic compounds

The synthesis of oxybenzone is shown below.



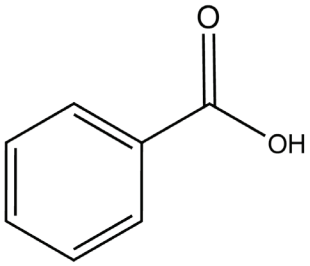
(c)

Draw the structures of compounds **A**, **B**, **C**, and **D**.

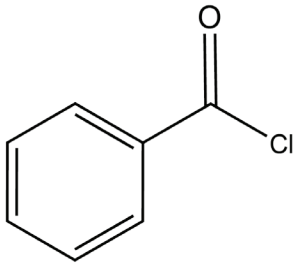
When you're done, turn over to check your answers.

Answers to RSC Chemistry Olympiad 2020 Round 1 Question 3

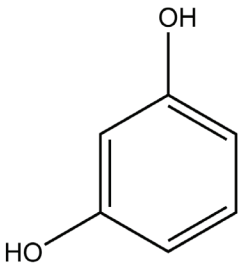
A



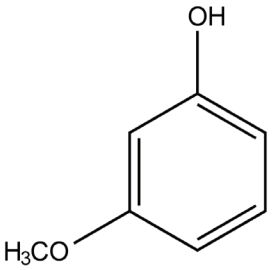
B



C



D



Further challenge

Challenge your understanding further with *UK Chemistry Olympiad 2010 round 1* question 1.

Worked answers explaining each step can be found in this UK Chemistry Olympiad Bite *https://edu.rsc.org/resources/chemistry-olympiad-bites-question-1-2010/1060.article*