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学生讲义

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Lecture 4 Organic Reaction

Test situation analysis

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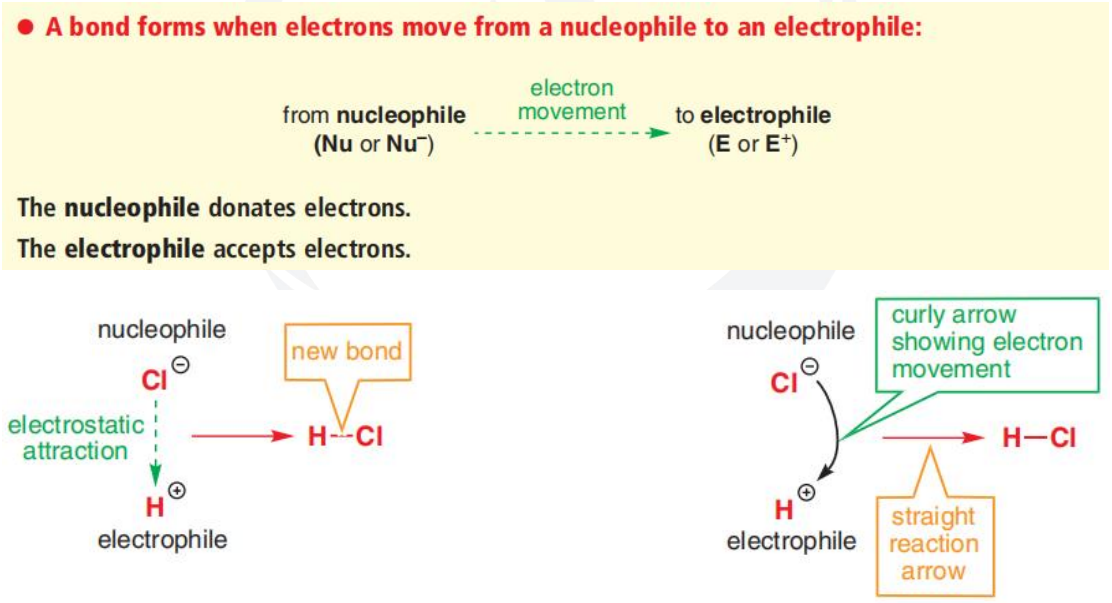
Nucleophilic substitution related to the carbonyl group		
Electrophilic addition to alkenes	25	Aromatic compounds
Electrophilic substitution on benzene		

Intensive Teaching and Practicing

Point 1：Nucleophile and Electrophile

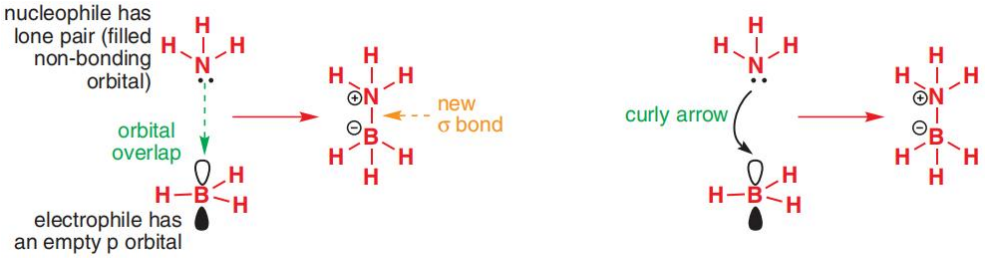
1.1 Reactions happen when electrons flow between molecules

When, as a result of these interactions, a pair of molecules find themselves close together, a reaction can take place provided electrons move from one molecule to another. This is what we call the mechanism of the reaction—the detailed description of the pathway the electrons take. In most organic reactions, the electrons start in one molecule and move towards another. We call the molecule which accepts the electrons the electrophile (electron-lover) . The molecule that donates the electrons is called the nucleophile.



Here's a very simple example that the nucleophile is an anion (Cl^-) and the electrophile is a cation (H^+). The two are brought together by charge attraction, and the new bond is formed by electrons donated by the nucleophile. Since we are representing the formation of a new bond by the movement of electrons, it's natural to use an arrow to show the way the electrons flow. Arrows used to show electron flow are always curved: we call them 'curly arrows'. The arrow showing the reaction itself is straight.

In the next example, neither the nucleophile (ammonia, NH_3) nor the electrophile (borane, BH_3) are charged, but they are drawn together by the interaction between theelectrons of the non-bonding lone pair at N and the empty *p* orbital on B. Electrons flow from the nucleophile (NH_3) to the electrophile (BH_3) and a new bond is formed.

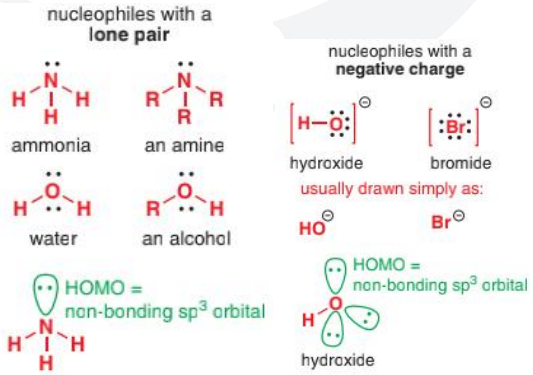


• The best nucleophiles have high-energy occupied molecular orbitals (HOMOs).

•The best electrophiles have low-energy unoccupied molecular orbitals(LUMOs).

1.2 Identifying a nucleophile

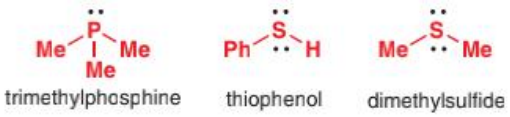
Nucleophiles are either negatively charged or neutral species with a pair of electrons in a high-energy orbital (the HOMO). The most common type of nucleophile has a non-bonding lone pair of electrons. Non-bonding electrons are typically high in energy because they do not benefit from the stabilization bonding electrons get from being shared between two nuclei. Typical neutral nucleophiles with lone pairs are ammonia, amines, water, and alcohols, all of which have lone pairs (one for N, two of equal energy for O) occupying sp^3 orbitals.



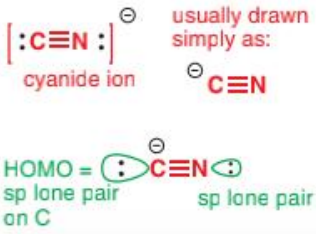
Other atoms later in the periodic table which carry lone pairs, such as phosphines, thiols, and sulfides, also make good nucleophiles, especially since their lone pairs are of even higher energy occupying orbitals made up of 3s and 3p atomic orbitals.

Anions which have lone pairs are often good nucleophiles too, partly because they can be attracted electrostatically by positively charged electrophiles. The anionic

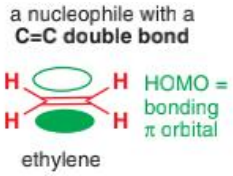
centre is usually O, S, or halogen, each of which can have several identical lone pairs. For example, hydroxide has three lone pairs—the negative charge cannot be assigned to one of them in particular. It's convenient just to draw the negative charge, and not the lone pairs as well. Negative charges like this actually represent a pair of electrons—both the 'extra' electron and its partner in the lone pair—so we normally write mechanisms with an arrow starting on the negative charge.



The most important carbon nucleophile with a lone pair of electrons is the cyanide ion. Although linear cyanide (which is isoelectronic with N_2) has a lone pair on nitrogen and a lone pair on carbon, the nucleophilic atom is usually anionic carbon rather than neutral nitrogen as the sp orbital on carbon is of higher energy than that on the more electronegative nitrogen, and therefore constitutes the HOMO.

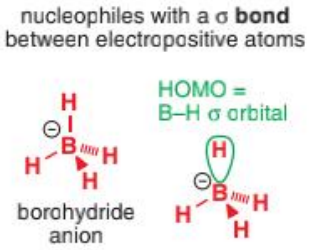


Molecules can still be nucleophilic without non-bonding lone pairs. The next highest set of orbitals are bonding π orbitals, especially C=C double bonds, since they are higher in energy than σ orbitals. Simple alkenes are weakly nucleophilic and react with strong electrophiles such as bromine. Note, however, that molecules with π bonds can also be electrophiles, particularly when the π bond involves an electronegative atom. The only common π nucleophiles are alkenes and aromatic rings. Finally, it is possible for the σ bond of a nucleophile to donate electrons, provided it is a σ bond associated with electropositive atoms such as B, Si, or the metals, along with C or H.

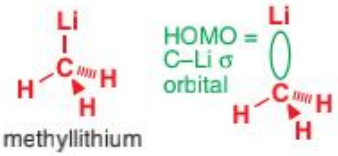


Borohydride is a good nucleophile—it attacks electrophilic carbonyl compounds, as you will see shortly. It donates electrons from its HOMO, the B–H σ bond. Notice that in this case the negative charge does not represent a pair of electrons: you cannot

start a curly arrow from it.

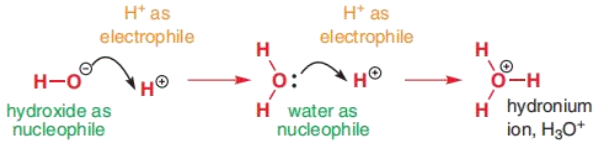


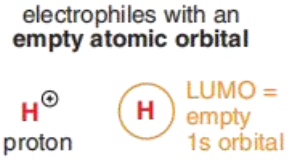
organometallics—compounds with carbon–metal bonds, for example methyllithium—acting as nucleophiles. They do so because the σ orbital generated from electropositive C and even more electropositive Li is high in energy.



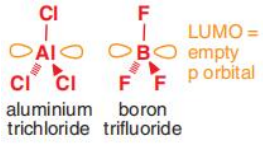
1.3 Identifying an electrophile

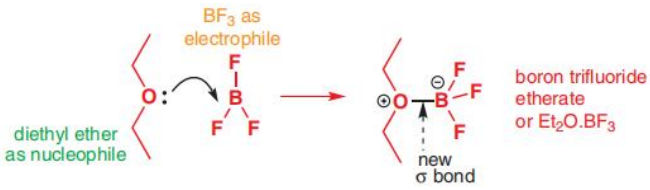
Electrophiles are neutral or positively charged species with an empty atomic orbital (such as the empty p orbital in borane) or a low-energy antibonding orbital that can easily accept electrons. The simplest electrophile is the hydrogen cation, H^+ , usually named for what it is, a proton. H^+ is a species without any electrons at all and a vacant, very low energy, 1s orbital. It is so reactive that it is hardly ever found and almost any nucleophile will react with it. Acid solutions containing H^+ are neutralized by the nucleophile hydroxide, for example, and strong acid goes on to protonate water as well, the water acting as a nucleophile and the proton as the electrophile. The product is the hydronium ion, H_3O^+ , the true acidic species in all aqueous strong acids. Here's the reaction between hydroxide and H^+ with the electron movement from the nucleophile to the electrophile represented by curly arrows. The arrows start on the hydroxide's negative charge, which represents one of the oxygen's pairs of electrons:





Other electrophiles with **empty atomic orbitals** include borane, and related compounds such as boron triflfl uoride and aluminium trichloride. BF_3 reacts with ethers, as shown below, to form stable complexes. This time the arrow starts on the lone pair.





the LUMOs are instead **low-energy antibonding orbitals associated with electronegative atoms**. These antibonding orbitals can be either π* orbitals or σ* orbitals—in other words, molecules which make good electrophiles might have a double or a single bond to an electronegative atom such as O, N, Cl, or Br.

Summary:This table can help you better distinguish nucleophiles and electrophiles

Nucleophile	Electrophile
Anion	Cation
Molecules have high-energy occupied molecular orbitals	Molecules have low-energy unoccupied molecular orbitals
Alkenes and benzene rings	C=O
Reducing agent	Oxidizing agent
Lewis bases	Lewis acids
Alkyl of organometallic compound	Alkyl of halogenoalkane

1.4 Reaction mechanism of nucleophilic substitution (S_N1&S_N2)

1.4.1 S_N1 (the unimolecular nucleophilic substitution mechanism)

S: substitution N: nucleophilic

Experiments show that the hydrolysis of tertiary halogenated hydrocarbons is carried out according to the single molecule substitution mechanism, and the reaction mechanism can be expressed step by step as follows:

$$R_3C\text{-}X \xrightarrow{slow} R_3C^+ + X^- \qquad \text{step 1}$$

$$R_3C^+ + OH^- \rightarrow R_3C\text{-}OH \qquad \text{step 2}$$

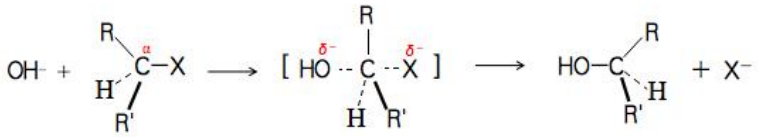
Step 1 is that the heterocleavage of C-X bond in halogenated hydrocarbons is carbon positive ions and halogen negative ions. However, unlike the dissociation of inorganic substances in water, halogenated hydrocarbons must be further polarized under the action of solvents before they can be heterocleaved into positive and negative ions. So this step is slow. Carbon positive ions are very unstable and will immediately combine with nucleophile OH^- in the solution to form alcohols.

In chemical reaction kinetics, the reaction rate is determined by the slowest step in the reaction. The first step in the above reaction mechanism is to determine the reaction rate. This step only depends on the fracture of C-X bond and has nothing to do with nucleophiles, so it is called single molecule mechanism.

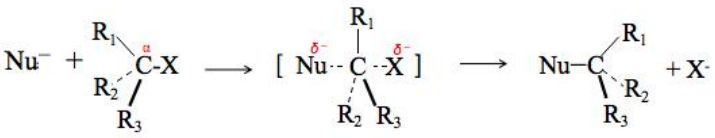
According to the single molecule mechanism, the reaction is carried out through the intermediate of carbon positive ions. The carbon positive ions are planar. When the carbon positive ions are formed, the OH - in the reaction system can be bonded with them from both sides of the plane, and the chances of bonding from both sides are equal. Therefore, when the carbon atom is a hand carbon atom and the reactant halohydrocarbon is a certain configuration in the optical isomer, Then the reaction product will be a racemic mixture, that is, 50% of the product has undergone configuration conversion, which is called racemization.

1.4.2 S_N2 bimolecular nucleophilic substitution

The bimolecular mechanism is characterized by the simultaneous breaking of C-X bond and the formation of C-O bond.



pentavalent trasition state



pentavalent trasition state

When the reaction is carried out according to the bimolecular mechanism, as shown in the previous reaction mechanism, OH^- attacks the carbon atom from the opposite side of the leaving group X. Only in this way, OH^- and X can be the furthest away, so as to minimize the mutual exclusion. When OH^- approaches α-C atom gradually, the three groups on α-C atom will be repulsed backward. In the transition state, OH^- is in a straight line with X and α-C atom, while the other three groups on the carbon atom are in the same plane perpendicular to the paper. With the combination of OH^- and α-C atom from the front, X^- leaves from the back, and α-C atom returns to tetrahedral shape, However, the three groups on α-C atom are reversed backward, and -OH is opposite to the original X. Therefore, the configuration of the generated alcohol has been transformed compared with the original halogenated hydrocarbon. **In the substitution reaction, the transformation of this configuration is called Walden transformation.**

1.4.3 The difference of S_N1 and S_N2: stereochemistry

The rate determining step in the S_N2 mechanism involves the nucleophile attacking the substrate whereas the rate determining step in the S_N1 mechanism involves the decomposition of the substrate without participation from the nucleophile.

One main difference in the 2 mechanisms is the stereochemistry of the product. The S_N2 reaction is stereospecific. That means the stereochemistry of the product is

dependent entirely on the stereochemistry of the substrate. Since the S_N2 reaction proceeds in a one-step fashion with a backside nucleophilic attack, there is an inversion in stereochemistry. The backside attack is due to the lone pair of electrons from the nucleophile donating into the σ*-orbital of the C–X bond, where X is the leaving group.

On the other hand, the S_N1 reaction is not stereoselective at all as it passes through a planar carbocation intermediate that may undergo nucleophilic attack from both sides with equal probability. Thus, an S_N1 reaction causes racemisation, forming an equal mixture of both enantiomers, known as a racemic mixture.

we show an example to demonstrate the stereochemical preference of nucleophilic substitutions using the 2 mechanisms.

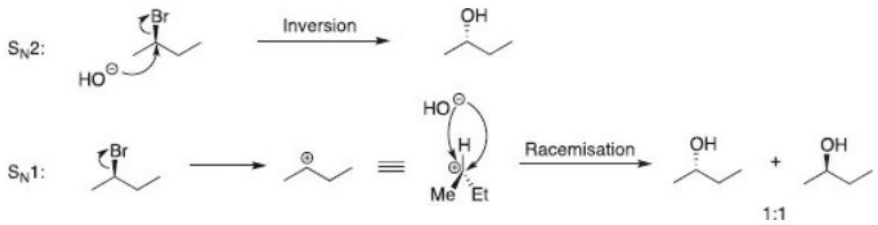


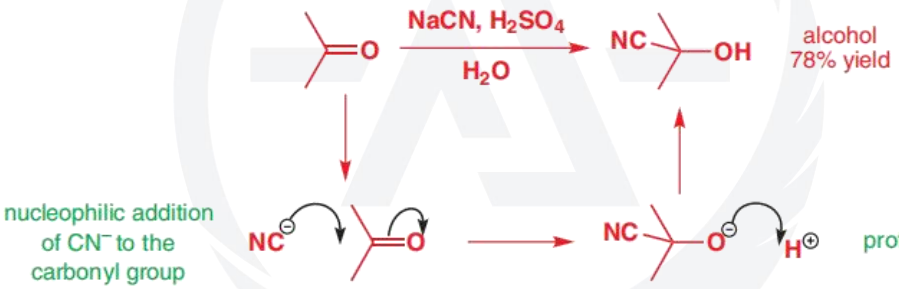
Fig . Stereochemical preference of **S_N2** and **S_N1** reaction mechanisms.

Point 2：Reaction mechanism related to C = O

2.1 Nucleophilic addition related to the carbonyl group

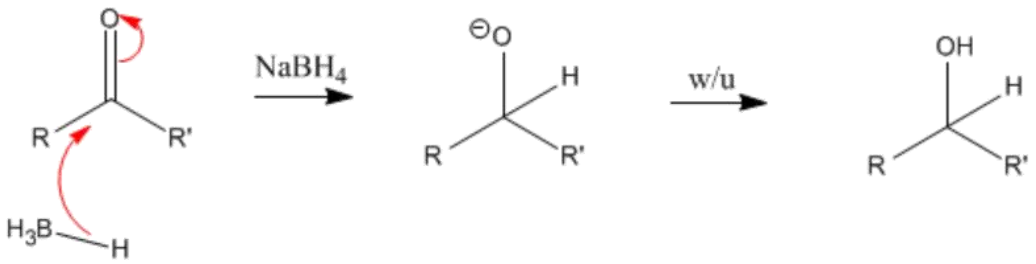
2.1.1 Nucleophilic addition of CN^- to carbonyl group

In this part we are going to concentrate on —probably the simplest of all organic reactions—the addition of a nucleophile to a carbonyl group. The carbonyl group, as found in aldehydes, ketones, and many other compounds, is without doubt the most important functional group in organic chemistry.The carbonyl group, C O, in aldehydes and ketones is polarised due to the high electronegativity of the oxygen atom. The electrons in the C=O bond are drawn nearer to the O atom, giving it apartial negative charge and leaving the C atom with a partial positive charge. This makes the C atom open to attack by a nucleophile, such as the cyanide ion, CN^-.



- Additions to carbonyl groups generally consist of two mechanistic steps:
  - nucleophilic attack on the carbonyl group
  - protonation of the anion that results.

2.1.2 Nucleohilic additon of hydride ion to carbonyl group(Reduction)

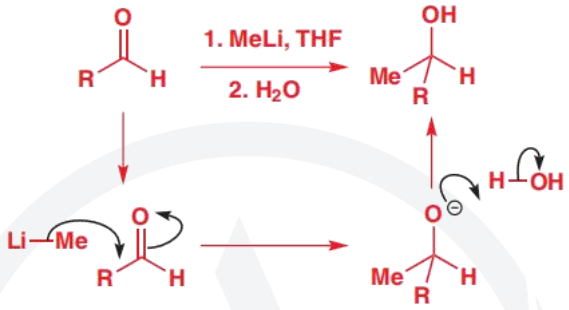


Only reacts with aldehydes and ketones,not the less react carbonyl compounds

2.1.3 Addition of organometallic reagents to aldehydes and ketones

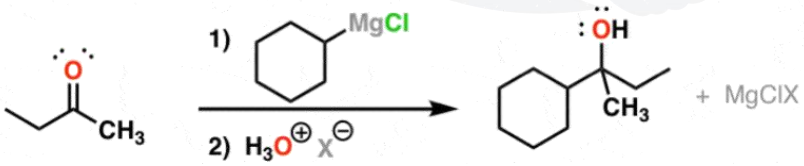
Grignard reagents

Organometallic compounds have a carbon–metal bond. Lithium and magnesium are very electropositive metals, and the Li–C or Mg–C bonds in organolithium or organomagnesium reagents are highly polarized towards carbon. They are therefore very powerful nucleophiles, and attack the carbonyl group to give alcohols, forming a new C–C bond.

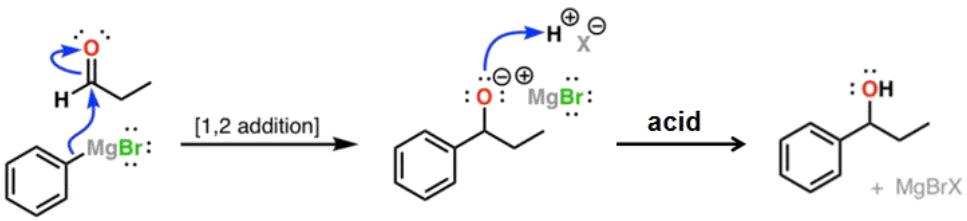


Organomagnesium reagents known as Grignard reagents (RMgX) react in a similar way. Some simple Grignard reagents, such as methyl magnesium chloride, MeMgCl, and phenyl magnesium bromide, PhMgBr. The reactions of these two classes of organometallic reagent— organolithiums and Grignard reagents—with carbonyl compounds are among the most important ways of making carbon–carbon bonds.

Example 1:Reaction with ketones to form tertiary alcohols

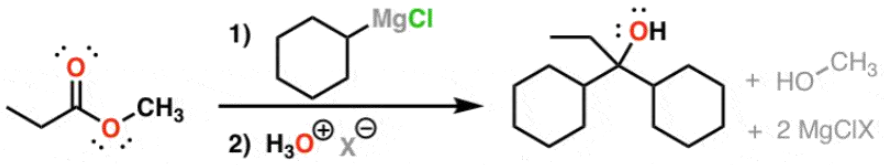


Example 2:Reaction with aldehydes to form secondary alcohols



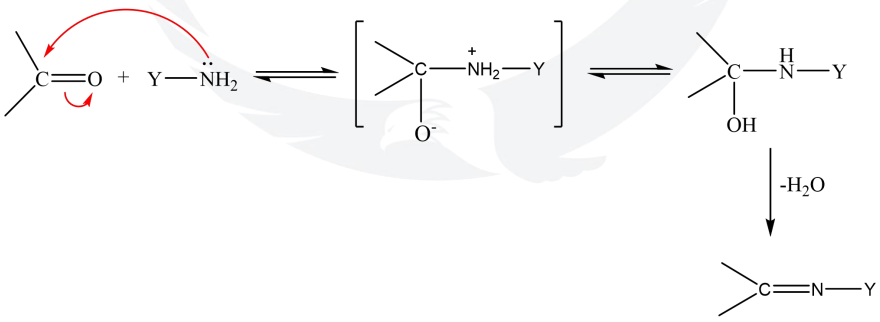
Example 3:Reaction with acid halides to give tertiary alcohols

Example 4:Reaction with esters to give tertiary alcohols



2.1.4 Addition condensation with ammonia derivatives

The N atom in the amino group combines with the carbonyl carbon atom with its lone pair electrons , and a pair of electrons of the carbon oxygen bond are transferred to oxygen to form an unstable intermediate. Once this intermediate is formed, the H^+ is immediately transferred from nitrogen to oxygen to form alcohol amine. The reaction does not stop at one-step addition reaction, but successively intramolecular dehydration to form C = N.



2.2 Nucleophilic substitution related to the carbonyl group

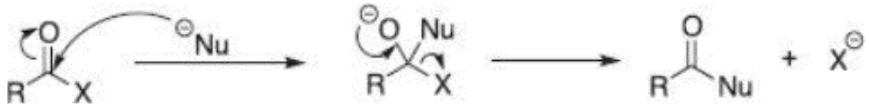
Nucleophiles add to carbonyl groups to give compounds in which the trigonal carbon atom of the carbonyl group has become tetrahedral.

These compounds are not always stable: if the starting material contains a leaving group, the addition product is a **tetrahedral intermediate**, which collapses with loss

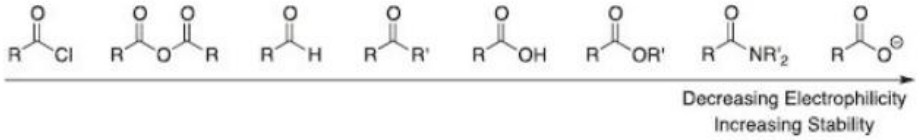
of the leaving group to give back the carbonyl group, with overall substitution of the leaving group by the nucleophile.

2.2.1 Nucleophilic substitution of carboxylic acid derivatives

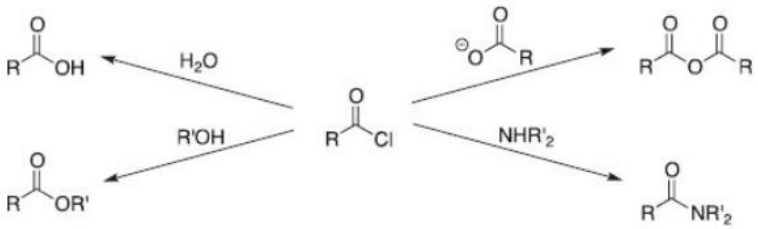
Carboxylic acid derivatives include acyl chlorides, acid anhydrides, esters and amides.General mechanism for nucleophilic substitution at carbonyl oxygen



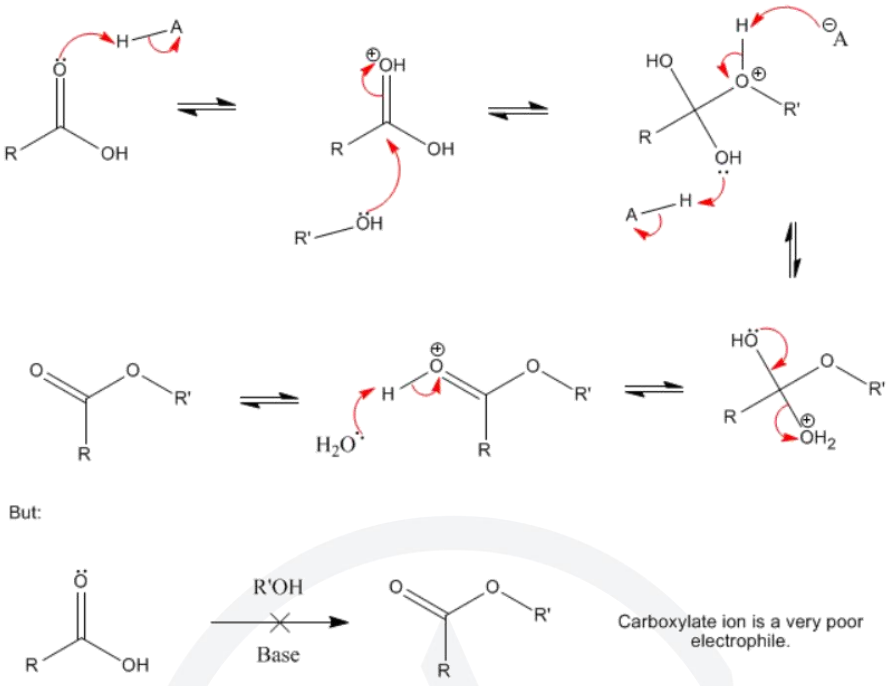
Reactivity series for carbonyl compounds:



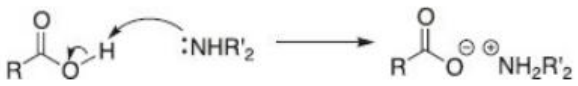
Reactions of acyl chlorides to form other carboxylic acid derivatives.



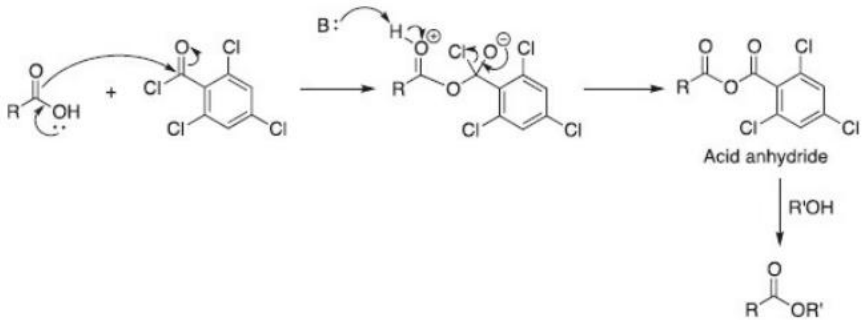
2.2.2 Mechanism of esterification:



☛Formation of salt from reaction of carboxylic acid with amine.



Reaction scheme for Yamaguchi esterification through acid anhydride intermediate:



☛Steglich esterification

One of the best nucleophilic catalysts is 4-(dimethylamino)pyridine, abbreviated as DMAP. The catalysed reaction pathway using DMAP is shown in Figure 4.7.39.

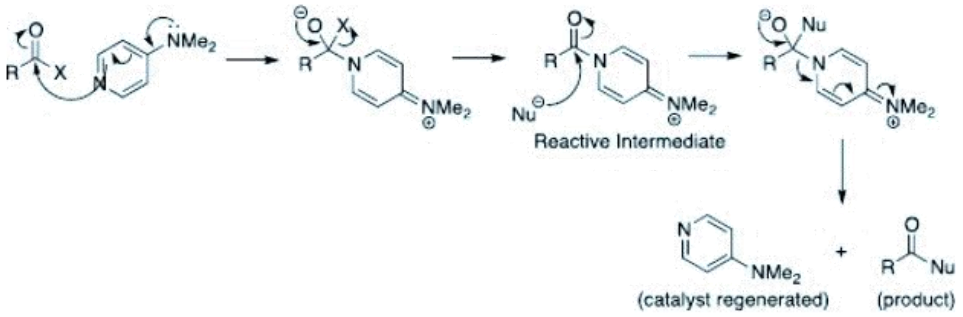
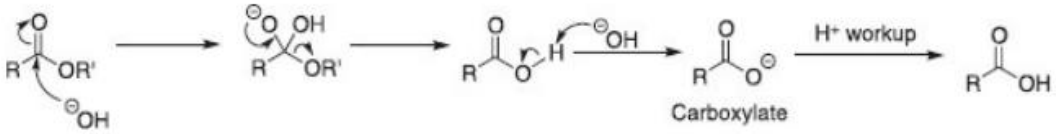


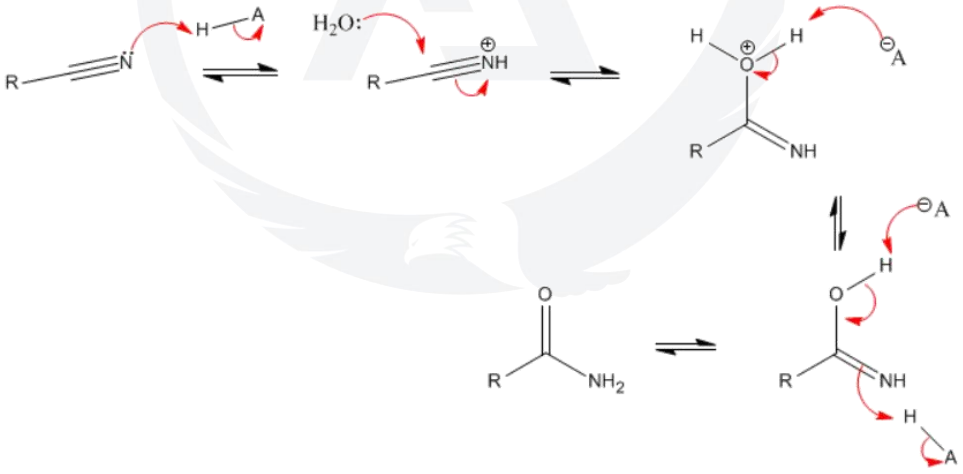
Fig . Reaction mechanism of catalysed nucleophilic substitution by DMAP.

2.2.3 Mechanism for basic hydrolysis :

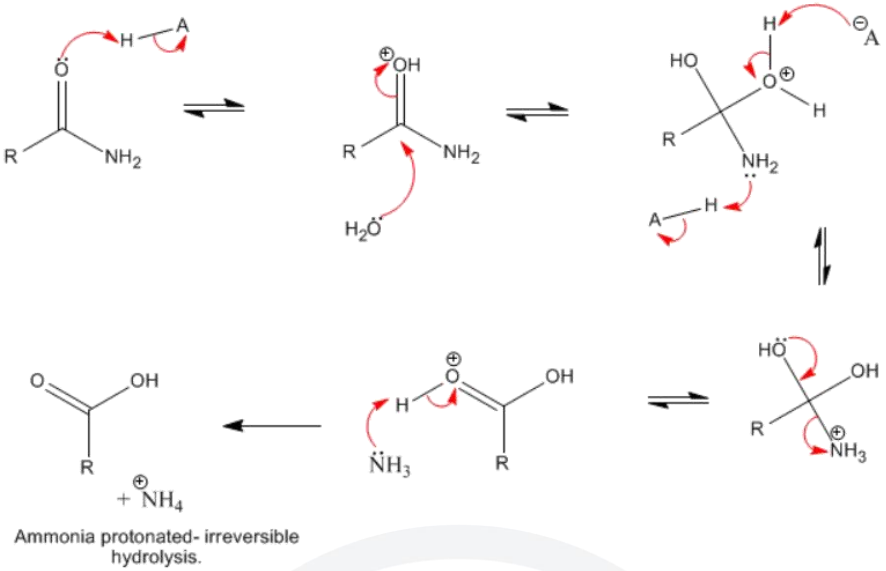
You can't make esters from carboxylic acids and alcohols under basic conditions because the base deprotonates the carboxylic acid. However, you can reverse that reaction and hydrolyse an ester to a carboxylic acid (more accurately, a carboxylate salt) and an alcohol.



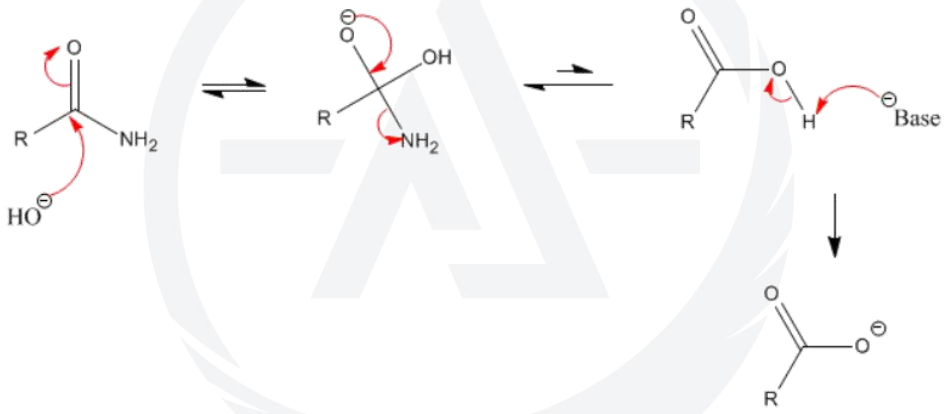
☛Mechanism for nucleophilc substitution-nitrile hydrolysis



☛**Mechanism for Nucleophilc substitution- amide hydrolysis (acid catalyst)**

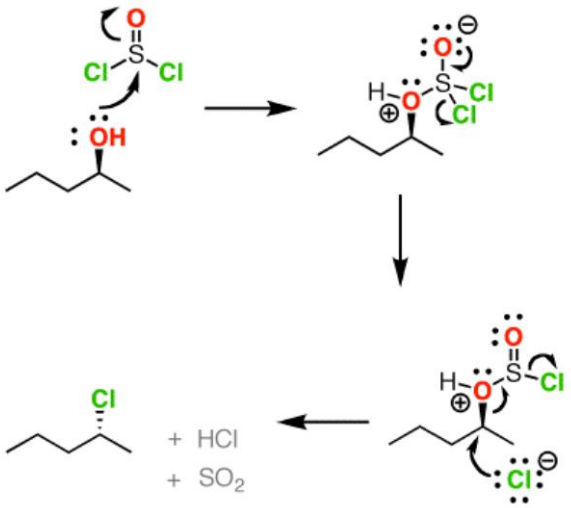


amide hydrolysis (base catalyst)

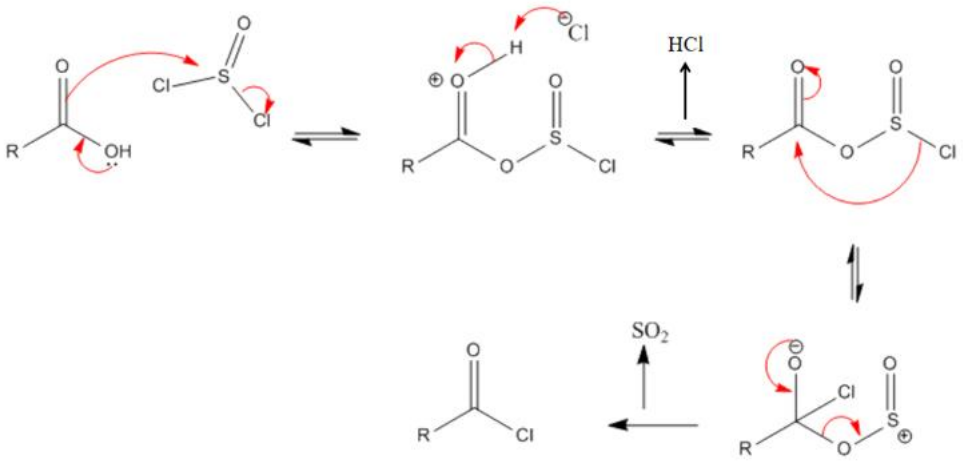


2.2.4 Nucleophilc substitution:Alcohol + $SOCl_2$ / carboxylic acid + $SOCl_2$

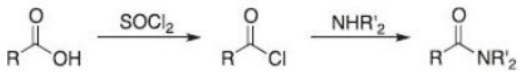
☛**Mechanism of conversion of acohols to chlorides with $SOCl_2$:**



☛Mechanism of conversion of carboxylic acids to acyl chlorides using $SOCl_2$:

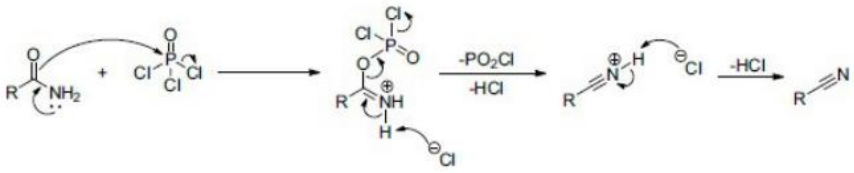


Possible synthetic route for amides through acyl chlorides:



➳Mechanism for dehydration of amide to nitrile with $POCl_3$

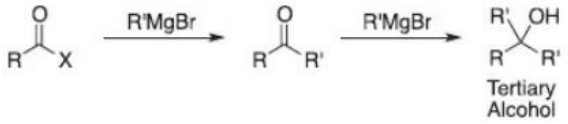
The reverse reaction to generate nitriles from carboxylic acid derivatives is the dehydration of amides. A commonly used dehydrating agent is $POCl_3$ and its mechanism for converting amides to nitriles is shown in the figure below.



2.3 How to achieve a clean conversion to ketone

It seems easy to prepare ketones from carboxylic acid derivatives through nucleophilic substitution using carbon nucleophiles. In reality, due to the high nucleophilicity of carbon nucleophiles such as Grignard reagents, the reaction does not stop at the ketone stage and the reagent will perform nucleophilic addition on the ketone to generate a tertiary alcohol, as shown in Figure (below figure).

Reaction of a carboxylic acid derivative with Grignard reagent:



This reaction is difficult to control, especially if the carboxylic acid derivative is less electrophilic than ketone. Thus, there are many methods developed to achieve a clean conversion to ketone.

1. Increasing electrophilicity and decreasing nucleophilicity.

We have previously learnt about Gilman reagents as soft organocopper reagents. Not only are they soft, they are also much weaker carbon nucleophiles than the common organolithium or Grignard reagents. They only perform nucleophilic attack at very electrophilic centres such as acyl chlorides, and do not react with ketones. Thus, we are able to obtain the ketone product by performing a nucleophilic substitution using **Gilman reagents** on **acyl chlorides**, as shown in Figure(below fig).

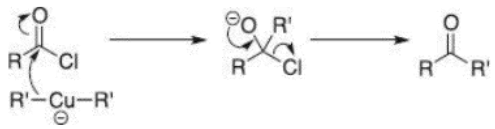


Fig . Mechanism for reaction of Gilman reagent with acyl chloride to form ketones.

2. Forming stable tetrahedral intermediates

Stable tetrahedral intermediates may be formed in certain special conditions. This means that the leaving group does not leave until the workup when the reaction is quenched. The tetrahedral intermediate is unable to undergo further nucleophilic attack by the carbon nucleophile and the strong carbon nucleophile is destroyed in the workup step.

One method to make use of stable tetrahedral intermediates is to use a large excess (>2 equivalents) of organolithium reagent when reacting with a carboxylic acid. The organolithium reagent will deprotonate the carboxylic acid, forming double oxoanions in the tetrahedral intermediate that are unable to act as leaving groups. This tetrahedral intermediate decomposes only upon workup, and all remaining organolithium reagent is destroyed.

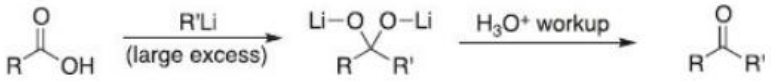


Fig . Stable tetrahedral intermediate formed from carboxylic acid with excess organolithium.

A more reliable method to generate a stable tetrahedral intermediate is through the use of Weinreb amides. Weinreb amides are specially designed amides with a methoxy group bonded to the amide nitrogen. This allows the metal to coordinate to both the methoxy group and the carbonyl oxygen in the tetrahedral intermediate, stabilising it through chelation. Since there are 2 ligands that may bind to the metal, a divalent metal will stabilise the intermediate best, and Grignard reagents with magnesium (2+) may be used as the nucleophile.

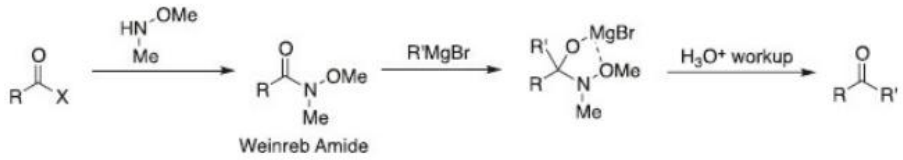
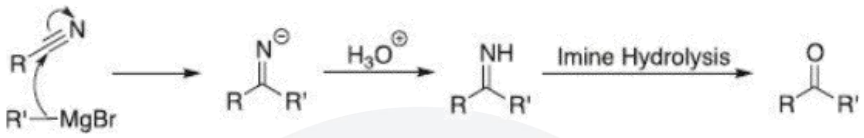


Fig . The preparation of Weinreb amide from carboxylic acid derivatives and its reaction with Grignard reagent.

It is worthy to note that amides may be easily prepared from the carboxylic acid derivatives as they are most thermodynamically stable, which also explains why the tetrahedral intermediate is stable. The amine can only leave after the acid workup protonates it, in the process destroying any excess Grignard reagent that may cause an over-addition.

3. Using nitriles

Nitriles are also electrophiles that can be prepared from dehydration of amides. They do not have a leaving group, thus they are unable to undergo nucleophilic substitution. Instead, **with Grignard reagents**, they undergo nucleophilic addition to form a deprotonated imine, which is no longer electrophilic due to the negative charge present on the nitrogen. Upon workup, the imine may be hydrolysed to ketone. This method prepares ketones without any risk of over-addition due to the reaction pathway following a nucleophilic addition mechanism.

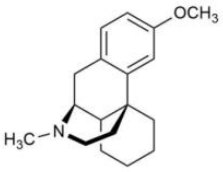


Preparation of ketones from nucleophilic addition to nitriles.

Example 1.*(source,UKChO,2018,4)*

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.

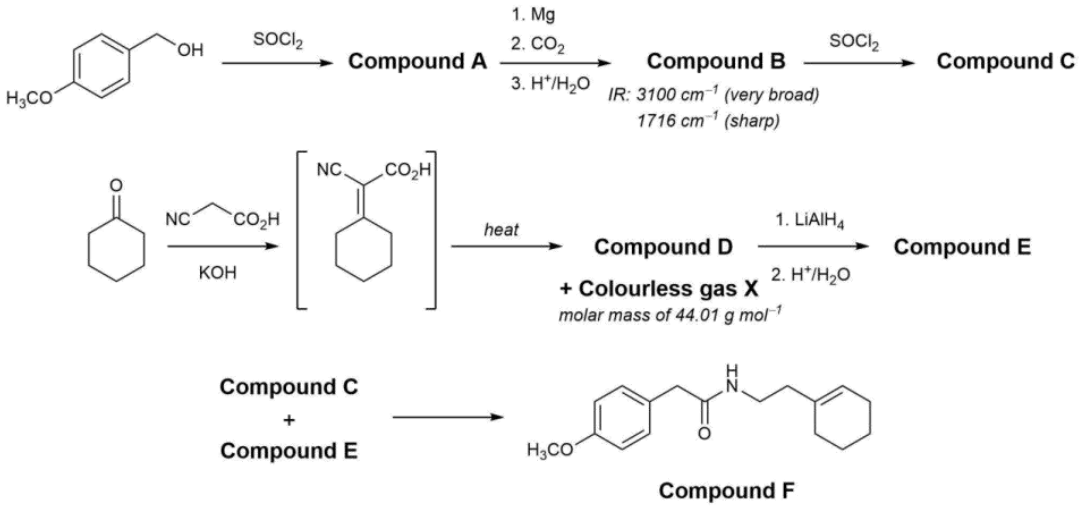
(a) In the answer book, circle the atom in dextromethorphan that is protonated in the salt.

(b) Determine the molecular formula of dextromethorphan and hence calculate the molar mass of the dextromethorphan hydrobromide monohydrate salt.

(Source,UKChO, 2018, 4c, 4d)

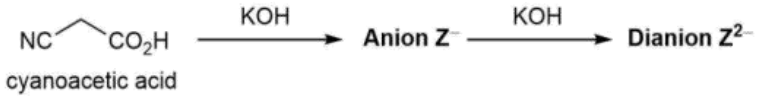
The synthesis of dextromethorphan takes a number of steps. Please note that in the schemes describing the synthesis, by-products of the reactions are not always shown.

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.

In the reaction to make compound **D**, the cyanoacetic acid can be deprotonated twice by the potassium hydroxide.

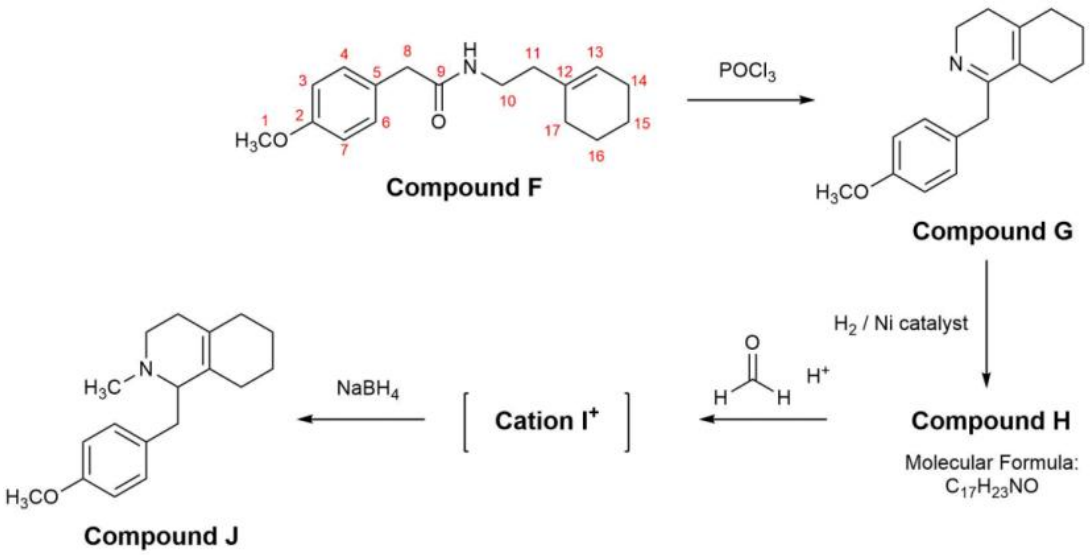


(d)(i) Draw a structure for anion Z^-.

(ii) Draw a structure for dianion Z^{2-}.

(source,UKChO, 2018, 4e, 4f)

The synthesis continues with the conversion of compound **F** to compound **J**.



(e) Write down the numbers of the two carbon atoms in compound F that are connected in the reaction to synthesise compound G.

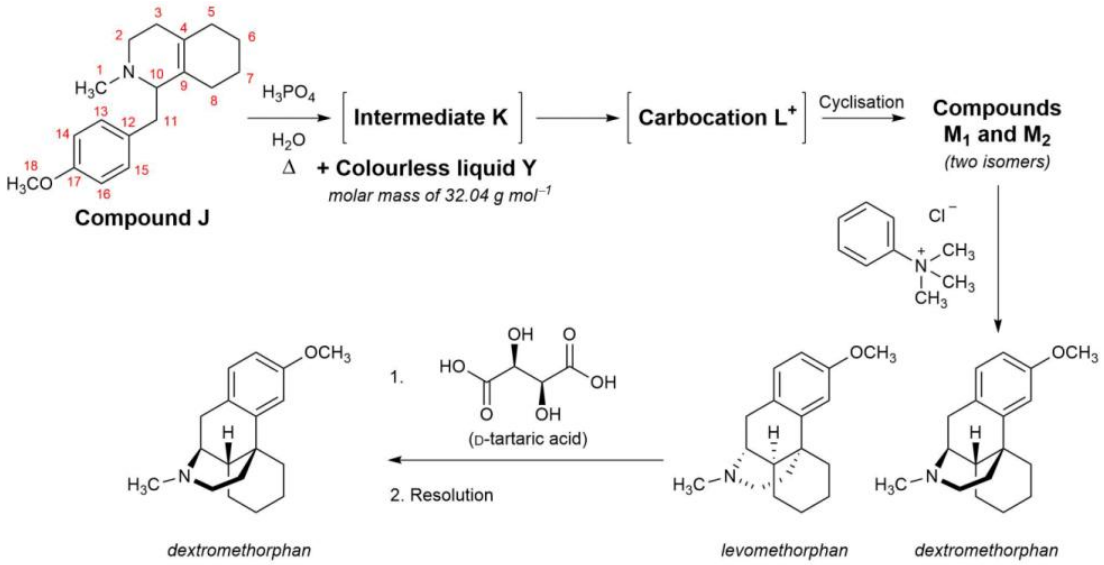
(f) Draw the structures of compound H and cation I^+

(source,UKChO, 2018, 4g-4i)

The synthesis continues with the conversion of compound J to compounds M_1 and M_2 in one step. Upon heating with aqueous phosphoric acid, compound J is first converted into intermediate K and a colourless liquid Y. Intermediate K is then converted to carbocation L^+, which undergoes cyclisation to give the mixture of the two isomers M_1 and M_2.

Treatment of the mixture of M_1 and M_2 with trimethylphenylammonium chloride (a methylating agent) gives a mixture of levomethorphan and dextromethorphan.

The addition of D-tartaric acid to this mixture allows the desired dextromethorphan to be separated from the undesired levomethorphan. This process is called resolution.



In the conversion of compound J to compounds $M_1$and M_2 it is possible for different pairs of carbon atoms to become connected.

(g) indicate all pairs of carbon atoms that can be connected in this reaction.

(h) Draw the strctures of intermediate **K**, carboncation $\mathbf{L}^+$ and liquid **Y**.

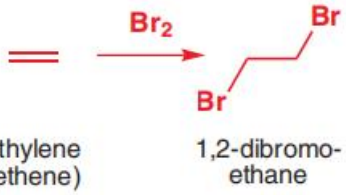
(i) complete the structures of the two isomers M_1 and M_2 indicating clearly any atoms other than hydrogen that come out of the plane of the paper (with wedged lines) and go into the plane of the paper (with dashed lines). State what type of isomers M_1 and M_2 are.

Point 3：Reaction mechanism related to alkene

3.1 Electrophilic addition to alkenes

3.1.1 Alkenes- electrophilic addition of Br_2

Bromine (Br_2) is brown, and one of the classic tests for alkenes is that they turn a brown aqueous solution of bromine colourless. Alkenes decolourize bromine water: alkenes react with bromine. The product of the reaction is a dibromoalkane, and the reaction below shows what happens with the simplest alkene, ethylene (ethene).

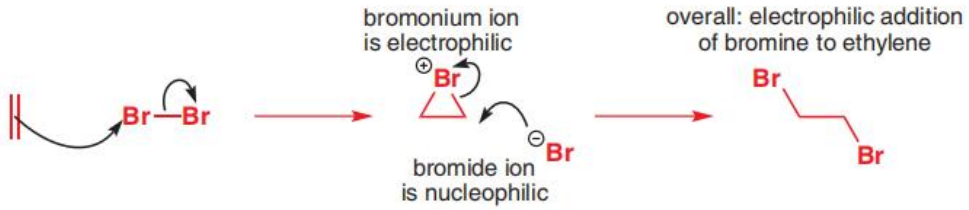


Br_2 has a low-energy empty orbital (the Br–Br σ*), and is therefore an electrophile. The Br–Br bond is exceptionally weak, and bromine reacts with many nucleophiles like this.

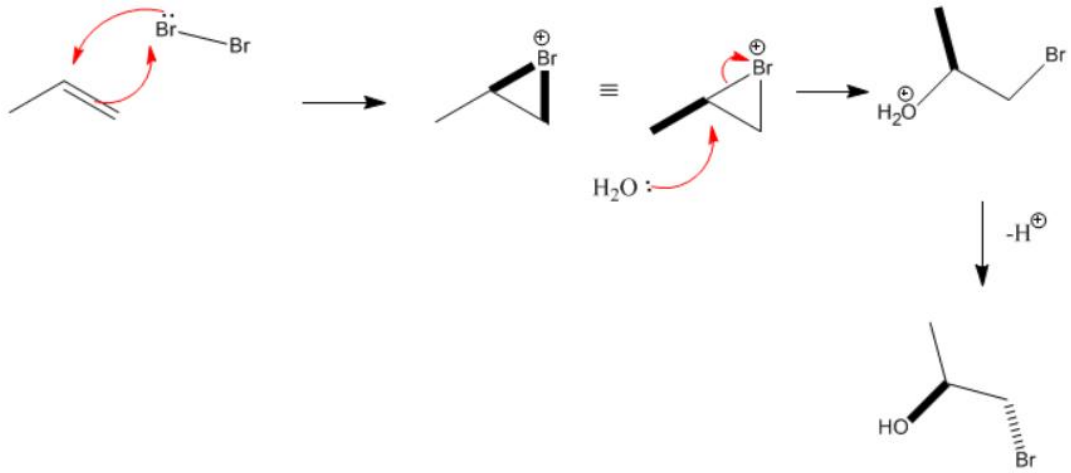
In the reaction with ethylene, the alkene must be the nucleophile, and its HOMO is the C=C π bond. Other simple alkenes are similarly electron-rich and they typically act as ***nucleophiles***.

When the addition of bromine and ethylene was carried out in the aqueous solution of sodium chloride, we found that there were also $BrCH_2CH_2Cl$ and $BrCH_2CH_2OH$ existed in the product. Because sodium chloride or water does not add with ethylene under this reaction condition, it shows that the addition of ethylene and bromine is carried out step by step, and the intermediate formed first should be positive ions.

We now draw the correct mechanism for the whole reaction.Since this addition reaction is caused by the attack of Br^+, that is, electrophile, So the reaction is called electrophilic addition.



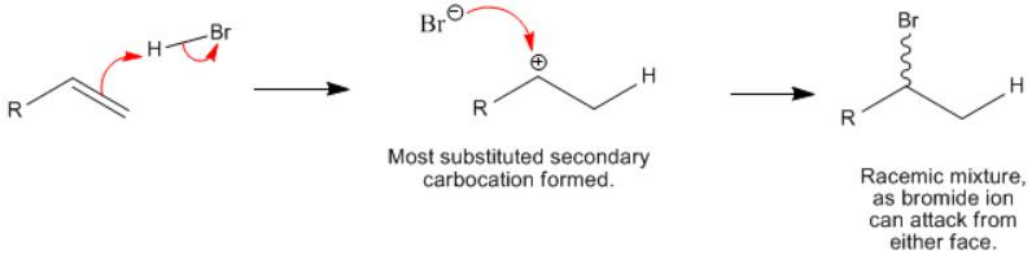
3.1.2 Alkenes-electrophilic addition to Br_2 and H_2O



3.1.3 Alkenes- electrophilic addition of HBr

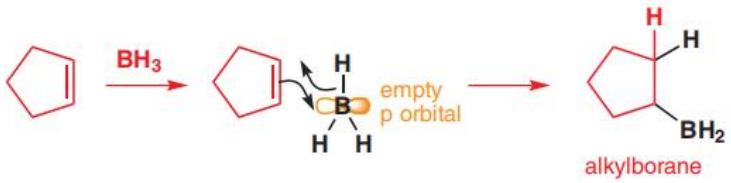
The addition of Alkenes and HX is also electrophilic addition. H^+ is first added to a carbon atom in the double bond(rate determination step), so that one of the carbon atoms has a positive charge to form a carbon positive ion, which is combined with X^-

$$HX \leftrightharpoons \mathbf{H^+} + X^-$$

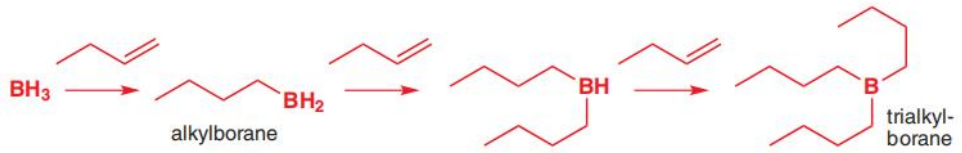


3.1.4 Alkenes- hydroboration

Boranes, including both BH_3 itself and analogues with one or two alkyl groups, HBR_2 , add to alkenes to make a new C–H bond and a new C–B bond by a mechanism we can write like this. The alkene pushes electrons into the boron's empty p orbital, while the hydrogen transfers onto the alkene.

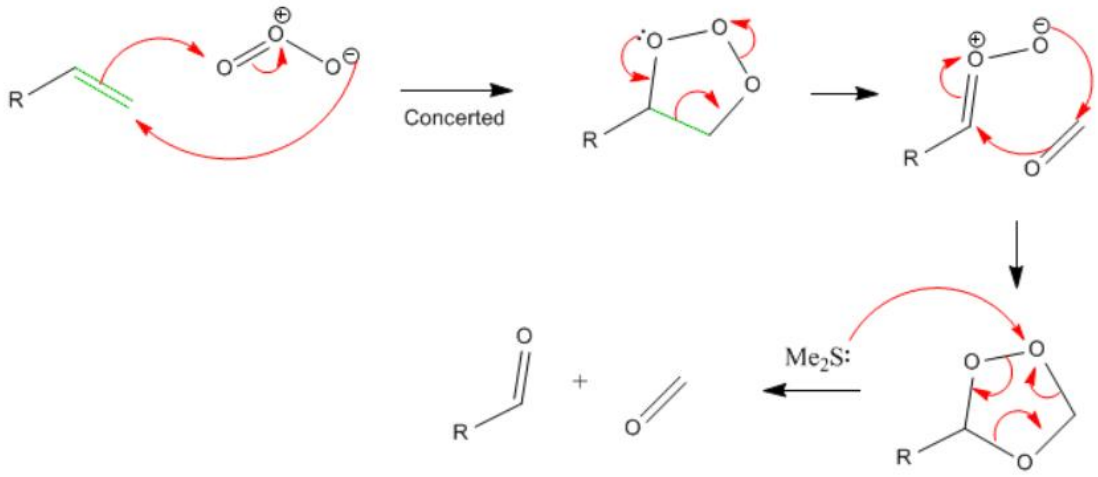


Importantly, if the alkene is unsymmetrical, the boron tends to end up on the less substituted carbon atom. This reaction can happen several times so, for example, if you start with an alkene and BH_3, you will typically end up with a trialkylborane:



3.2 Alkenes- ozonolysis

Ozone is unstable, and is generated immediately before use from oxygen (using a device called an 'ozonizer') and bubbled into the reaction mixture. Like OsO_4, it adds to alkenes by a cyclic mechanism: the product is a fivemembered ring with three oxygen atoms. It is extremely unstable and collapses by breaking a weak O–O bond and a C–C σ bond, but gains two strong C=O bonds in the process.



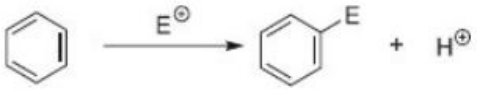
Point 4：Reaction mechanism related to benzene

Electrophilic substitution only happens on aromatic compounds.

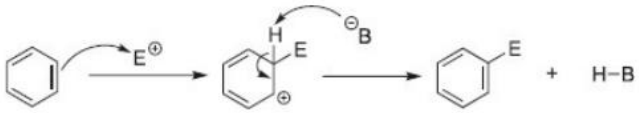
4.1 Electrophilic substitution on benzene

4.1.1 The reaction and mechanism of electrophilic aromatic substitution on benzene

The most common aromatic structure we encounter is benzene. Due to its aromaticity, it is highly unreactive. The most common reaction for benzene is electrophilic aromatic substitution.



General mechanism for electrophilic aromatic substitution:



The main challenge in electrophilic aromatic substitutions is to have a good enough electrophile to initiate the reaction. Unlike electrophilic addition mentioned in the previous point, benzene is a much less reactive nucleophile than alkenes due to the high energy penalty required to destroy aromaticity. In the next part, we will discuss **methods** to **generate common electrophiles for electrophilic aromatic substitution.**

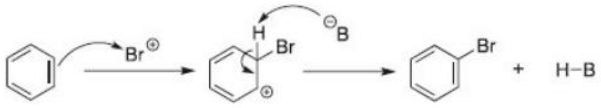
4.1.2 Electrophilic substitution on benzene-Halogenation

Firstly, for halogenation reactions, the halogen is no longer a good enough electrophile for reaction. We need to generate a halogen cation by adding a Lewis acid to the halogen.

Mechanism for generation of halogen cation:

Common Lewis acids employed for this purpose are $AlCl_3$ and $FeBr_3$. The halogen cation can proceed to react with benzene in an electrophilic aromatic substitution reaction as shown in Figure 4.10.5. Note that this method of halogenation is only possible for chlorides and bromides.

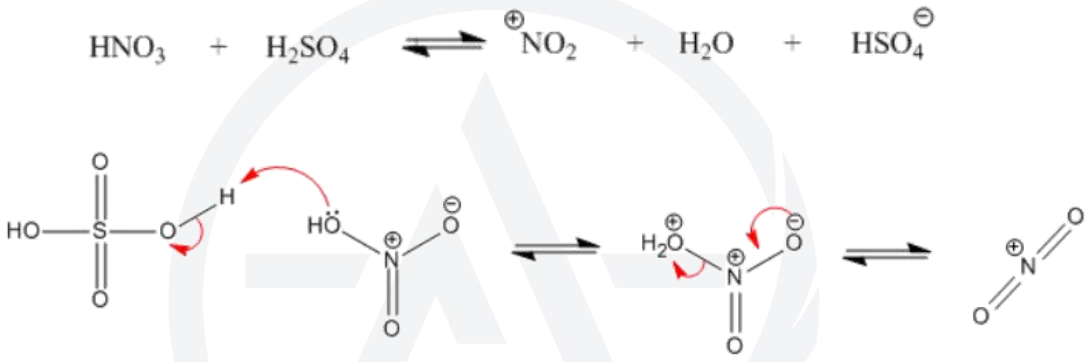
Mechanism for halogenation of benzene with halogen cation:



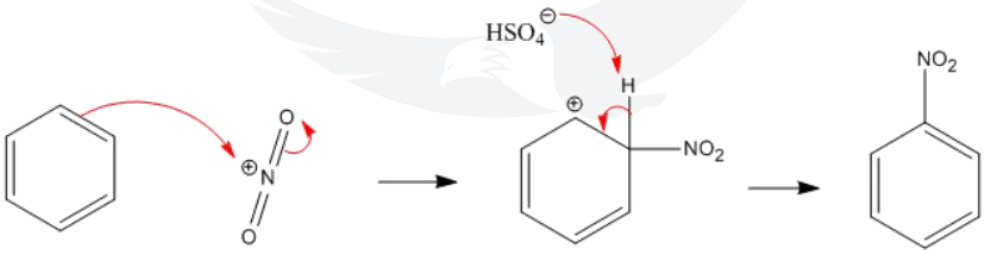
4.1.3 Electrophilic substitution on benzene-Nitrification

Next, we will look at nitration of benzene rings. Nitration requires harsh conditions, as the nitronium cation NO_2^+ must be formed as the electrophile. This is achieved by using a mixture of concentrated nitric acid and concentrated sulfuric acid as shown in the figure below.

Mechanism for formation of nitronium ion:



The nitronium ion may proceed to react with benzene through the same electrophilic aromatic substitution mechanism:



Nitration of benzene is a highly useful reaction as this forms a C–N bond. The nitro group may be reduced to an amino group, with many possible reaction conditions developed for this reduction.

The classic method is using tin in hydrochloric acid, however, other methods, such as catalytic hydrogenation and reduction with $LiAlH_4$, have been reported.

The amine may further react to form a diazonium salt, which is a reactive intermediate that undergo further substitution reactions, such as the Sandmeyer

reaction. The full reaction scheme is shown in Figure.

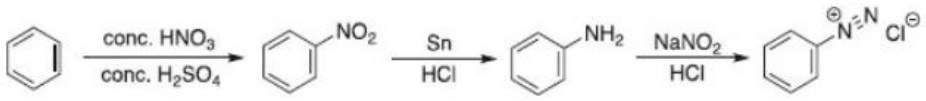
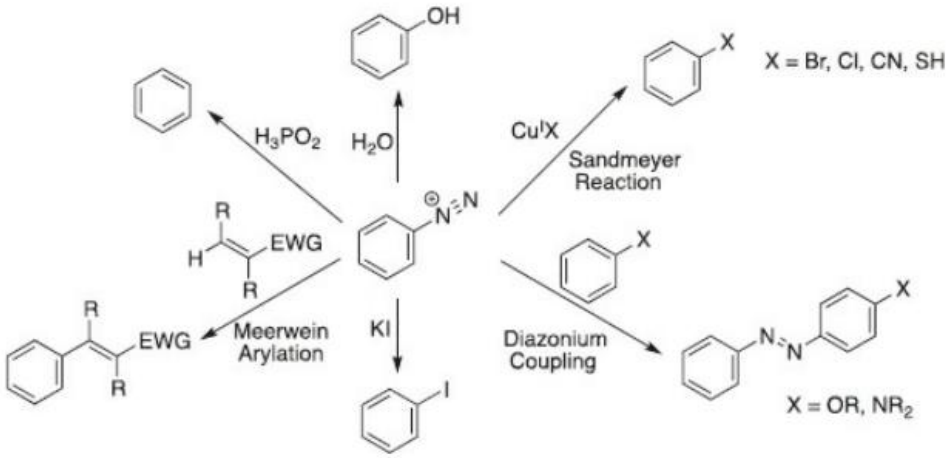
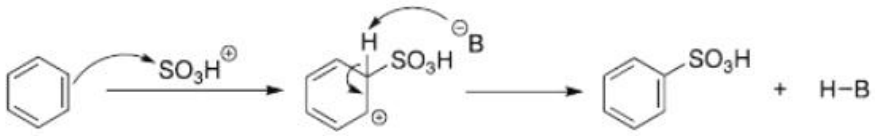


Fig . Full reaction scheme for formation of diazonium ion.

Reactions of diazonium arene:



4.1.4 Electrophilic substitution on benzene-sulfonation:

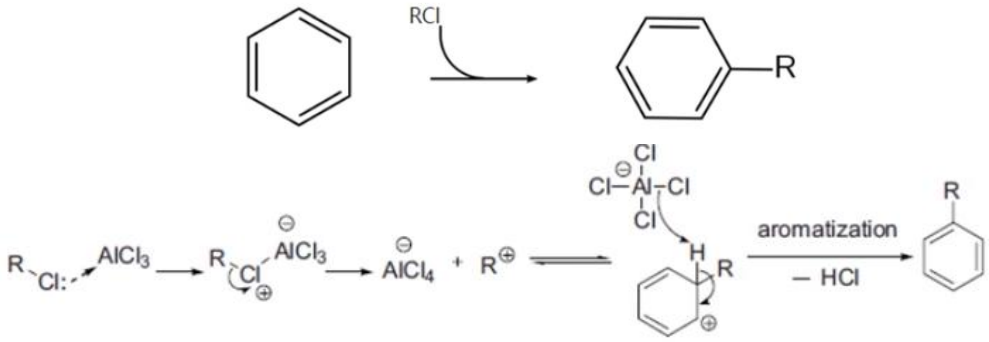


4.2 Friedal-Crafts reactions

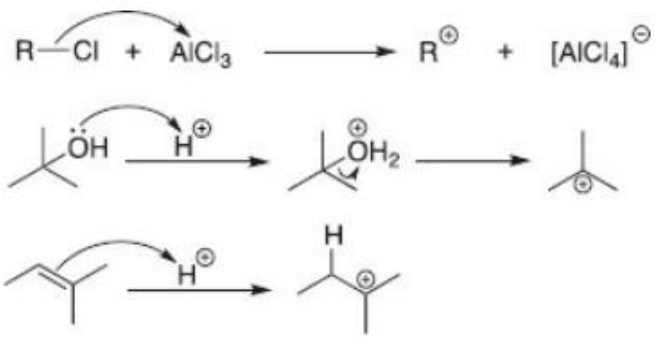
Up to now, we have discussed many reactions that provide us with many paths to aromatic C−X bonds, where X are heteroatoms, especially through diazonium arene intermediate. However, we have yet to discuss formation of C−C bonds, the backbone of organic chemistry. This can be done through **Friedal-Crafts reactions.** This consists of **Friedal-Crafts alkylation** and **Friedal-Crafts acylation.**

4.2.1 Electrophilic substitution on benzene-Friedal-Crafts alkylation:

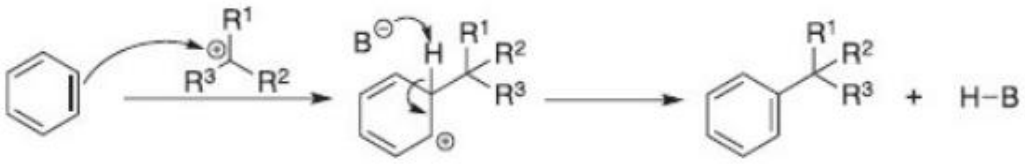
We will first look at Friedal-Crafts alkylation.



In this reaction, the cation is a carbocation, as a C−C bond must be formed. The carbocation may be generated using acids, and a range of possibilities are shown in Figure below.



Theoretically, we would expect these cations to react with benzene through the same electrophilic aromatic substitution mechanism as we have seen for many reactions above. General mechanism for the Friedal-Crafts alkylation of benzene:

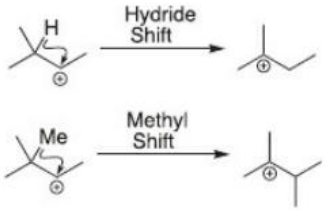


Ideally, the reaction may be carried out with large scope of R1, R2 and R3. However, in reality, there are many concerns for the Friedal-Crafts alkylation, and we will discuss the 2 main concerns here:

1. Unstable carbocations rearrange readily

unstable carbocations will undergo rearrangement to shift the positive charge to a more substituted carbon centre that increases the stability of the carbocation. We will

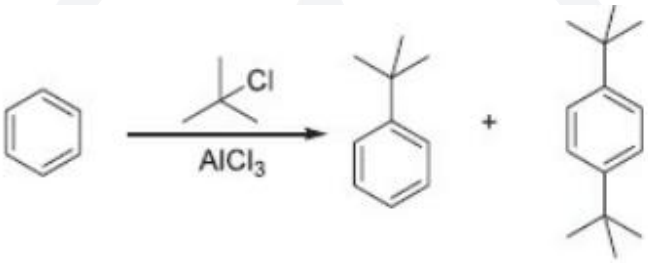
look at the most common carbocation rearrangements, which involves hydride shift and methyl shift. Examples of hydride and methyl shift:



2. Friedal-Crafts alkylation usually leads to over-substitution

As alkyl groups activate and make the benzene ring more reactive, the benzene ring is likely to undergo further substitution to form both mono- substituted and multi-substituted products, as shown in Figure 4.10.17. The next section will discuss in detail the substituent effects on the benzene ring.

Friedal-Crafts alkylation will often lead to over-substitution:

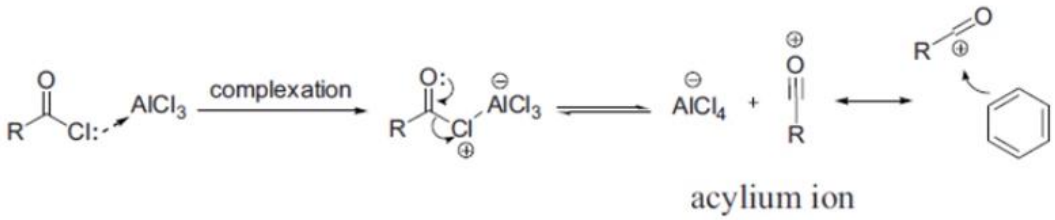


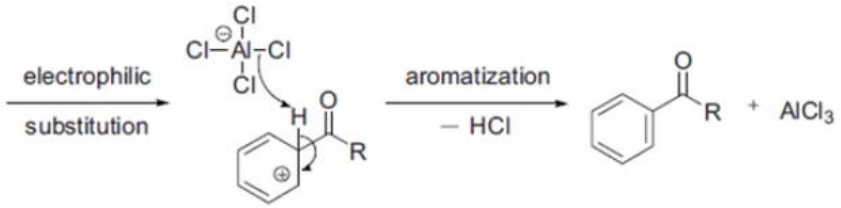
4.2.2 Electrophilic substitution on benzene-Friedal-Crafts acylation:

Due to the limitations of Friedal-Crafts alkylation, Friedal-Crafts acylation is the preferred method for preparation of aromatic C−C bonds.

Friedal-Crafts acylation allows the carbocation to be stabilised by the adjacent oxygen, forming the acylium ion intermediate. The acylium ion intermediate is more stable and does not rearrange readily.

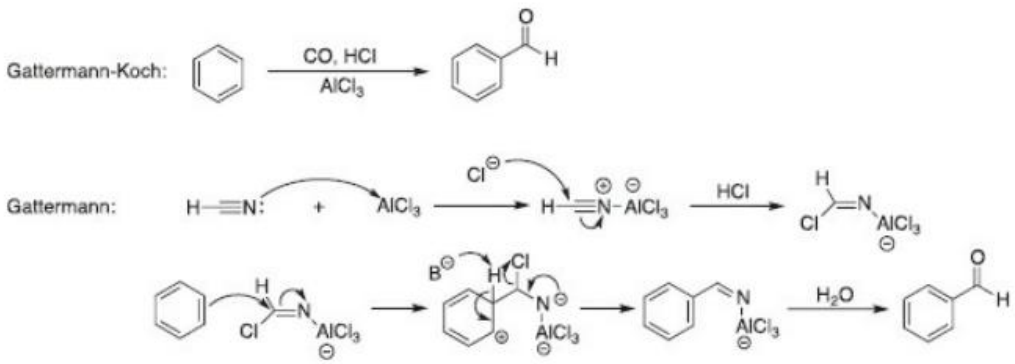
Mechanism for Friedal-Crafts acylation of benzene:





The only limitation for the Friedal-Crafts acylation is that methanoyl chloride, HCOCl, is unstable and may not be used as a reagent in Friedal- Crafts acylation. Thus, it is difficult to formylate benzenes. To do that, we may employ the Gattermann or Gattermann-Koch reaction.

The Gattermann-Koch reaction is essentially a Friedal-Crafts acylation using HCOCl, however, the HCOCl is formed in-situ from CO and HCl. The Gattermann reaction avoids HCOCl completely, using a nitrogen derivative by adding HCN and HCl to the reaction mixture. Formylation reactions of benzene:



4.3 Substituent effects of electrophilic substitution on benzene

Now that we have discussed the main electrophilic aromatic substitution reactions on benzene, we will move on to consider substituent effects. In electrophilic aromatic substitution reactions, benzene acts as a nucleophile by attacking with electrons from its aromatic system. Thus, it is a better nucleophile if the ring is more electron-rich. This can be achieved by attaching electron-donating substituents to the ring, activating the ring. On the other hand, addition of electron-withdrawing substituents to the ring will decrease the electron density in the ring, deactivating the ring. Thus, electron-donating groups are able to significantly speed up the electrophilic aromatic substitution while electron-withdrawing groups slow down the reaction.

4.3.1 Localization law of substituents on benzene ring (localization effect or orientation effect)

According to a large number of experimental results, some common groups can be divided into two categories according to their localization effects:

1. Ortho and para positioning group (first type of positioning group)

The following groups belong to this group:

$-N(CH_2)_2$ $-NH_2$ $-OH$ $-OCH_3$ $-NH-\overset{\overset{O}{\|}}{C}-CH_3$

$-O-\overset{\overset{O}{\|}}{C}-CH_3$ $-CH_3(R)$ $-X(-Cl,-Br)$ $-CH_3COOH$

If one of the above groups has been carried on the benzene ring, when the substitution reaction is carried out, the second group mainly enters its ortho and para position, and the product is mainly two binary substitution products of ortho and para position. For example, the bromination of bromobenzene and the nitration of toluene mentioned above are mainly mixtures of o-P isomers.

2. Meta positioning group (type II positioning group)

The following groups belong to this group:

$-N^+(CH_3)_3$ $O=N^+=O$ $-C\equiv N$ $-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-OH$ $-\overset{\overset{O}{\|}}{C}-H(R)$ $-\overset{\overset{O}{\|}}{C}-OH$

If one of the above groups is connected to the benzene ring, and then the substitution reaction is carried out, the second group mainly enters its meta position.

For example, the nitration product of nitrobenzene is mainly m-dinitrobenzene.

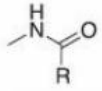
From the structure of the above two groups, the following empirical laws can be summarized: Generally speaking, if the atom directly connected to the benzene ring in the group has an unsaturated bond or positive charge, this group is a meta positioning group. On the contrary, it is an adjacent para positioning base. However, there are exceptions, such as - CH = CH_2 is the ortho positional base, and - CCl_3 is the meta positional base.

The introduction of o-para positioning groups into the benzene ring can make the benzene ring easier to undergo electrophilic substitution reaction, that is, they can activate the benzene ring. For example, toluene is more easily nitrated than benzene because of the activation of methyl.

The meta positioning group has a blunt effect on the electrophilic substitution of the benzene ring. When these groups are connected to the benzene ring, it is difficult for the electrophilic substitution reaction of the benzene ring. If nitrobenzene continues to nitration, higher reaction conditions are required than benzene. Although halogens belong to ortho para positioning groups, they are blunt to benzene rings.

Table 4.15 ranks the electronic effects of substituents from the most activating to the most deactivating.

Table 4.15. Activating and directing effects of substituent groups.

Activating effect	Substituent group	Directing effect
Strongly Activating	$—O^{\ominus}$	ortho, para
Strongly Activating	$—NR_2$, $—NH_2$	ortho, para
Strongly Activating	—OR, —OH	ortho, para
Activating		ortho, para
Activating	—R (Alkyl)	ortho, para
Deactivating	Halogens: F > I > Cl ≈ Br	ortho, para
Deactivating	—CN	meta
Deactivating	$—SO_3R$	meta
Deactivating	$—CO_2R$, $— CO_2H$	meta
Deactivating	—COR, —CHO	meta
Strongly Deactivating	$—CF_3$	meta
Strongly Deactivating	$—NO_2$	meta

The rankings on the table follow the electron-donating and electron- withdrawing effects of the substituent groups. The only interesting fact to draw our attention to is the halogens. Halogens are electron-withdrawing through the inductive effect due to

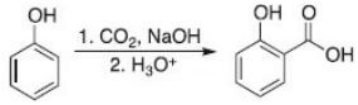
their high electronegativity, but electron- donating through the resonance effect.

We would expect fluorine to be the most deactivating as it has the highest electronegativity, and for the electron- withdrawing inductive effect to decrease with electronegativity down the group. In fact, fluorine is the least deactivating because the resonance effect, where the 2p lone pair is donated into the benzene ring, is the most significant. The extent of the resonance effect depends on the overlap between benzene orbitals and the halogen orbitals, and the orbital overlap is more effective when the orbitals are of similar size, in the case of 2p-2p overlap for fluorine.

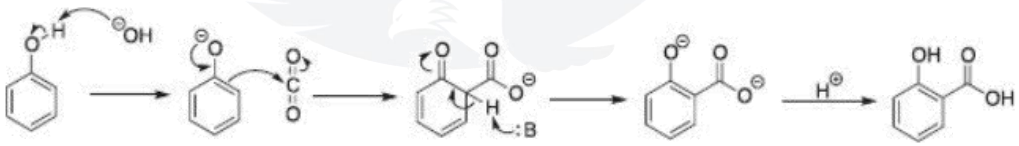
The other irregularity for halogens is that they are electron-withdrawing substituents that deactivate the benzene ring, but they direct further substitution at the ortho and para positions. This is again due to the resonance effect where the halogen is able to donate electrons from its lone pair tostabilise the cation adjacent to it.

One famous method of preparing salicylic acid: the Kolbe-Schmitt process

Highly activated benzene rings, such as phenol, can react with weaker electrophiles. One famous method of preparing salicylic acid, the Kolbe-Schmitt process (Figure 4.10.23), utilises the high reactivity of phenol to efficiently synthesise salicylic acid.



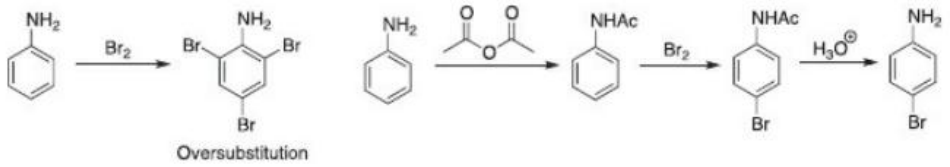
The mechanism of the Kolbe-Schmitt process follows electrophilic aromatic substitution with carbon dioxide as the electrophile:



Prevent over-substitution: protect the amine by using acetic anhydride

While high reactivity due to activating substituents may allow more reaction pathways, it may also lead to unwanted reactions. This happens when electrophilic aromatic substitution reactions are carried out on aniline, as the amino group is strongly activating. To prevent over-substitution, we may protect the amine by using acetic anhydride to make it less activating.

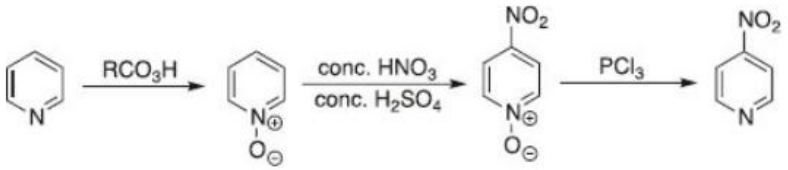
Scheme to protect amine on aniline to avoid oversubstitution:



4.4 Electrophilic aromatic substitution on aromatic heterocycles

Generally, pyridine is too electron-deficient to undergo the electrophilic aromatic substitution reactions mentioned in this chapter. To perform electrophilic aromatic substitution on pyridine, we need to activate it by oxidising it to pyridine N-oxide. The oxidation is usually carried out by a peroxyacid. The pyridine N-oxide is more electron-rich due to the strongly electron-donating oxide substituent. It is able to undergo the electrophilic aromatic substitution reactions stated in this chapter. To reduce the pyridine N-oxide back to pyridine, we may use a phosphine such as PCl_3 due to the strong P=O bond that can be formed. A sample reaction scheme for nitration is shown in Figure 4.10.26.

Reaction scheme for nitration of pyridine through pyridine N-oxide:



It is much easier to carry out electrophilic aromatic substitution on electron-rich heterocycles. These are 5-membered ring heterocycles with one heteroatom. The most reactive in this group is pyrrole, as nitrogen is the most strongly electron-donating. Furan is less reactive than pyrrole, while thiophene is the least reactive in the group, having similar reactivity to benzene. The general scheme for the electrophilic aromatic substitution of such heterocycles is shown in Figure 4.10.27.

Fig . General scheme for electrophilic aromatic substitution on pyrrole.

Notice that the electrophile is regioselectively added to the 2nd or 5th carbon of pyrrole, not the 3rd or 4th. To understand the regioselectivity of the reaction, we must examine the mechanism carefully as shown in Figure 4.10.28.

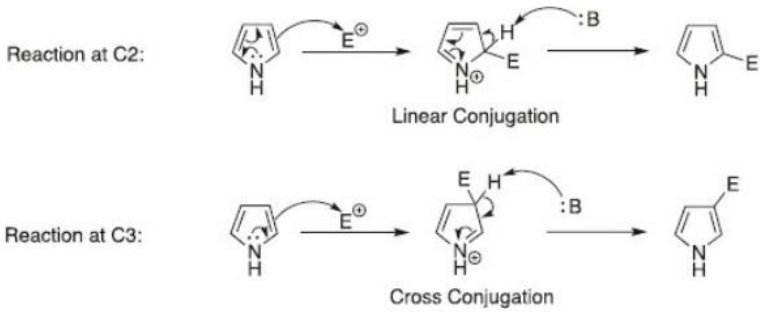


Fig . Mechanisms for electrophilic aromatic substitution at different positions

Reaction at the 2nd carbon gives a linearly conjugated intermediate cation, which is more stable than the cross-conjugated cation intermediate for a reaction at the 3rd carbon. We will look at the formylation of such heterocycles, through the Vilsmeier reaction. This reaction may be applied to benzene as well, but it is more commonly used on pyrrole. Figure 4.10.29 shows the general reaction scheme for the Vilsmeier reaction.

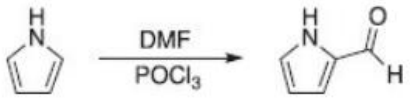


Fig . General reaction scheme for Vilsmeier reaction on pyrrole

The first reaction happens between N,N-dimethylformamide (DMF) and $POCl_3$ to generate the electrophile that reacts with pyrrole through electrophilic aromatic substitution. The full mechanism is shown in Figure 4.10.30.

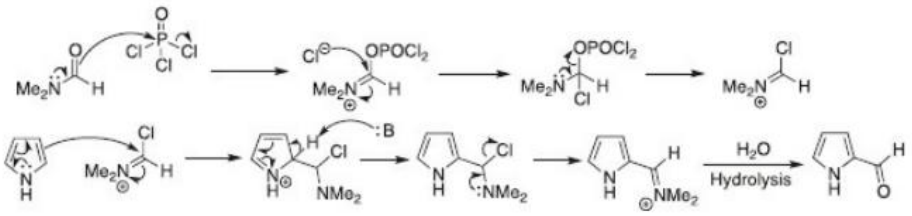
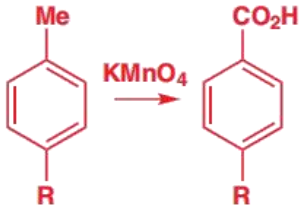


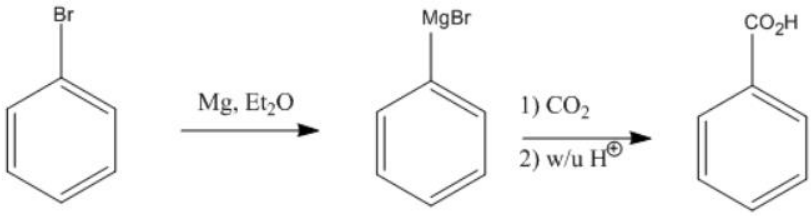
Fig . Mechanism for Vilsmeier reaction on pyrrole.

4.5 Formation of benzoic acid

Potassium permanganate is a very powerful oxidant and will also oxidize a benzylic methyl group (i.e. a toluene derivative) to a carboxylic acid.



Extention:



Summary

1.Nucleophile and Electrophile

● **A bond forms when electrons move from a nucleophile to an electrophile:**

from **nucleophile** (**Nu** or **Nu⁻**) —electron movement→ to **electrophile** (**E** or **E⁺**)

The nucleophile donates electrons.
The electrophile accepts electrons.

Nucleophiles are either _____ charged or neutral species with a pair of _____in a high-energy orbital (the HOMO).

Electrophiles are neutral or _____ charged species with an empty atomic orbital (such as the empty p orbital in borane) or a low-energy antibonding orbital that can easily accept electrons.

2.Reaction mechanism of nucleophilic substitution (S_N1&S_N2)

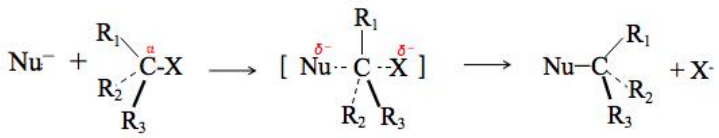
SN1:

For example:

$R_3C\text{-}X \rightarrow R_3C^+ + X^-$ step 1

$R_3C^+ + OH^- \rightarrow R_3C\text{-}OH$ step 2

SN2:



pentavalent trasition state

3.Nucleophilic addition&substitution related to the carbonyl group

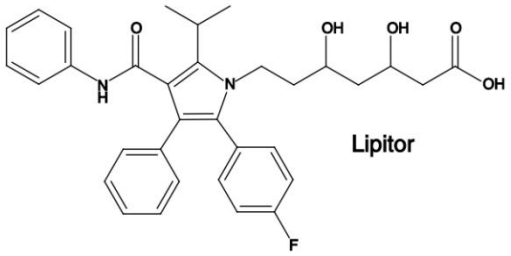
4.Electrophilic addition to alkenes

5.Electrophilic substitution on benzene

QUIZ

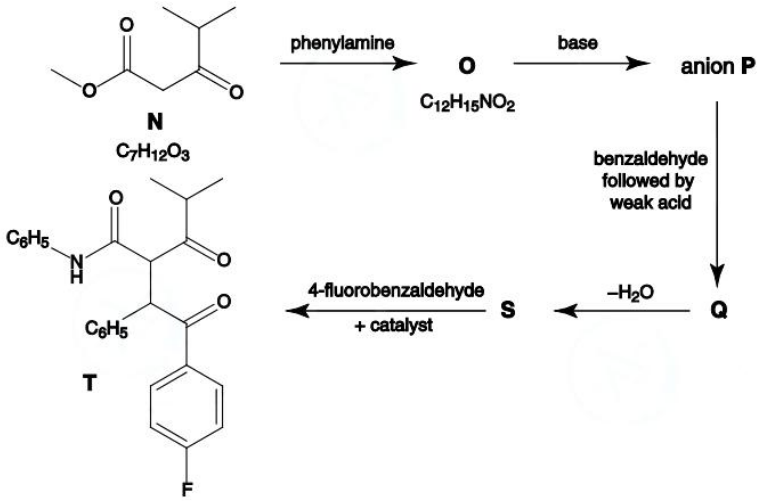
Question 1.*(source,UKChO,2012,4d-4e)*

This question is about the synthesis of top-selling drug Lipitor®



Lipitor

In a separate branch of the synthesis, **N** reacts with phenylamine to give compound **O**. This may be deprotonated in base to give another carbon nucleophile, anion **P**. Anion **P** reacts with benzaldehyde to give **Q** ; **Q** then dehydrates to give compound **S**. **S** reacts with fluorobenzaldehyde in the presence of a catalyst to give compound **T**.



(d) Give the structures of phenylamine and 4-fluorobenzaldehyde.

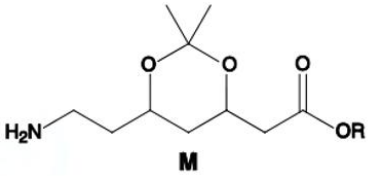
(e) Suggest structures for **O**, anion **P**, and compounds **Q** and **S**.

(source,UKChO,2012,4f)

In the final stage of the synthesis, **T** and **M** are brought together to give compound **U** which on hydrolysis in aqueous acid gives the target, the drug Lipitor.

Previous conclusion:

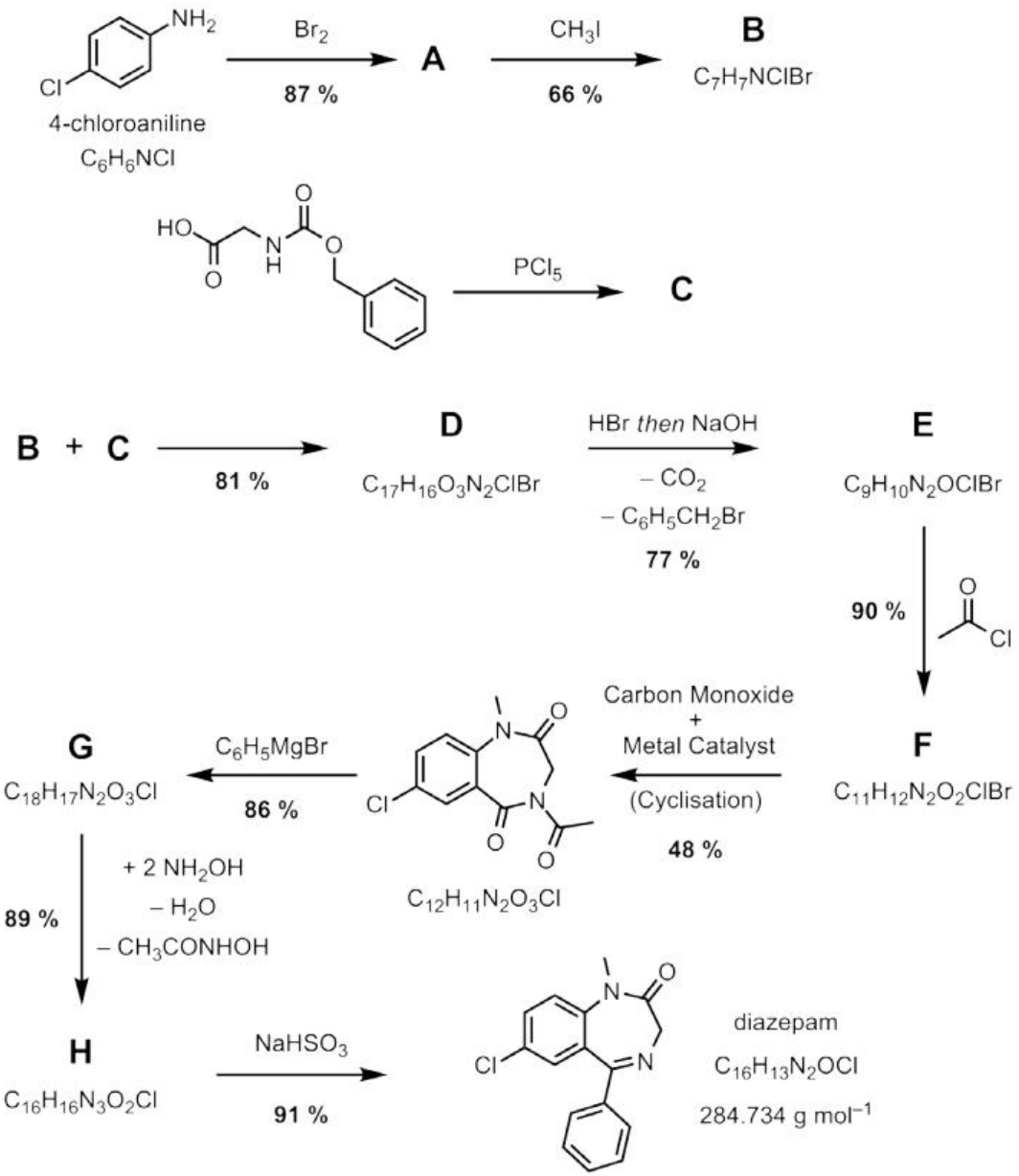
The structure of M：



M

Question 2. ***(source,UKChO,2013,4a-4b)***

The synthesis of diazepam from 4-chloroaniline is shown below. The percentage yield for each step is also shown. By-products are not always shown.



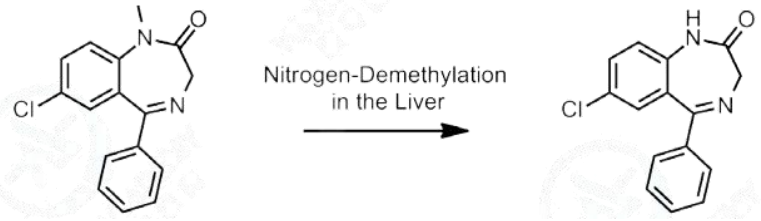
(a) (i) Calculate the overall percentage yield for the conversion of 4-chloroaniline to diazepam.

(ii) A patient was prescribed diazepam for three years at a dose of 5 mg, four times a day. Calculate the mass of diazepam this was, and hence the mass of 4-chloroaniline needed to make the drug for this patient.

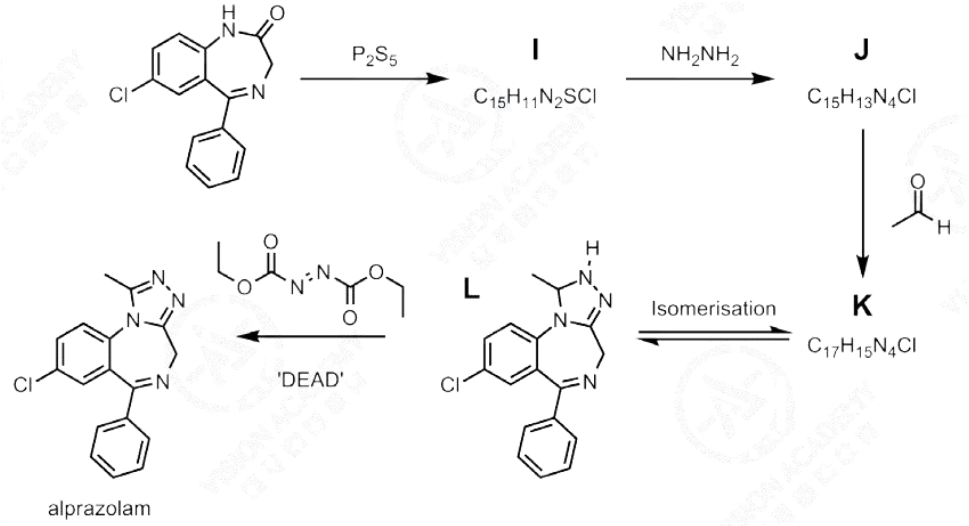
(b) Draw the structures of intermediates **A** – **H** in the synthesis of diazepam.

Source,UKChO, 2013, 4c-4d

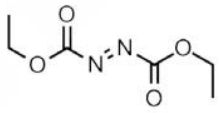
In the liver it was found that diazepam underwent a demethylation reaction. The product of this demethylation reaction was used as inspiration for the synthesis of the drug alprazolam.



(c) The synthesis of alprazolam is shown below. Draw the structures of intermediates **I**, **J** and **K**



(d) In the final stage of the synthesis, compound **L** is treated with a chemical called 'DEAD' to convert it into alprazolam. DEAD stands for diethyl azodicarboxylate. How would you classify the reaction of **L** to alprazolam using one of the terms below?



'DEAD'

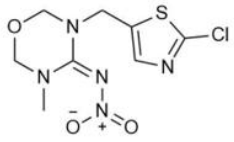
Tick the correct answer in your answer booklet.

Isomerisation **Hydrolysis** **Condensation** **Oxidation** **Reduction**

Question 3.*(source,UKChO,2019,4a-4b)*

This question is about bees and Brexit

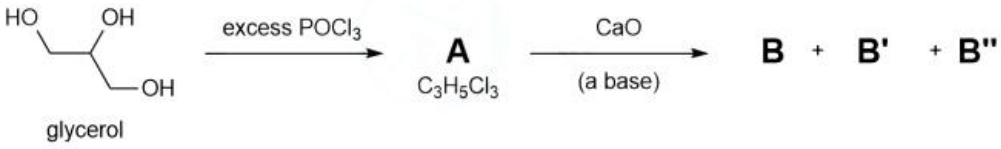
There is concern that neonicotinoid pesticides are harmful to bees. Thiamethoxam is one of three neonicotinoids that the European Union (EU) banned from all outdoor uses in April 2018. When Britain leaves the EU, this pesticide may become available for use in the UK again. People are worried this will harm our bee population.



thiamethoxam

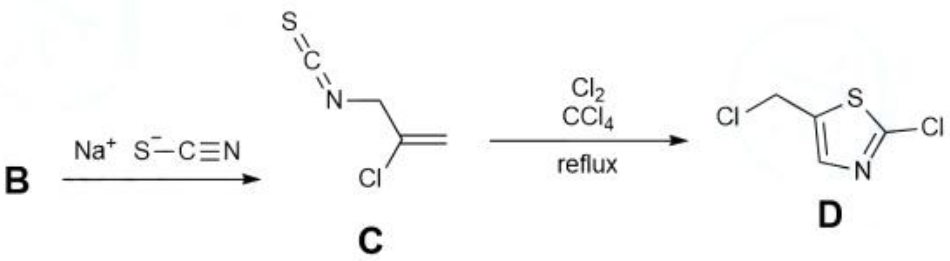
(a) What is the molecular formula of thiamethoxam?

The synthesis of thiamethoxam begins with glycerol. In the conversion of **A** to **B**, two other side products (**B'** and **B''**) can also be formed. **B**, **B'** and **B''** are isomers. **B'** and **B''** are geometric isomers. Much less **B''** is formed than **B'**.



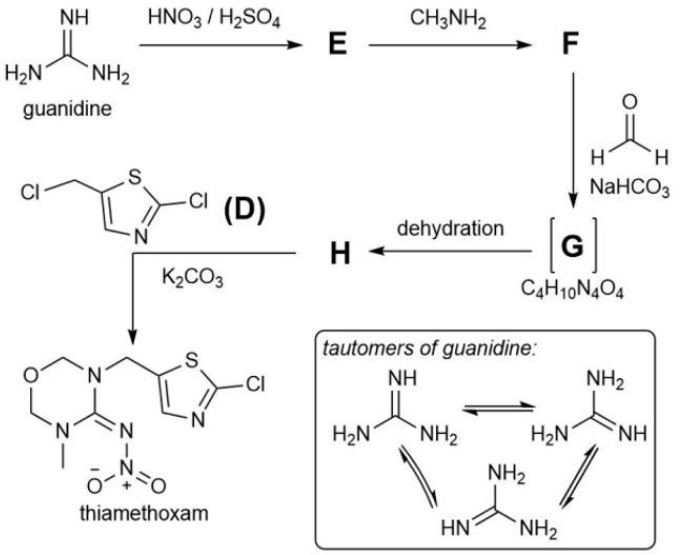
(b) Draw the structures of **A**, **B**, **B'** and **B''**.

B reacts with sodium thiocyanate (NaSCN) to form **C**, which can be converted into **D** upon treatment with chlorine and carbon tetrachloride.



Question 4.*(source,UKChO,2019,4d-4e)*

The remainder of the synthesis begins with guanidine.
Guanidine exists as one of three equivalent tautomers,which are all in rapid equilibrium with each other. Tautomers are isomers that only differ in the position of hydrogen atoms and double bonds.
Each intermediate (E, F, G and H) can also exist as different tautomers.

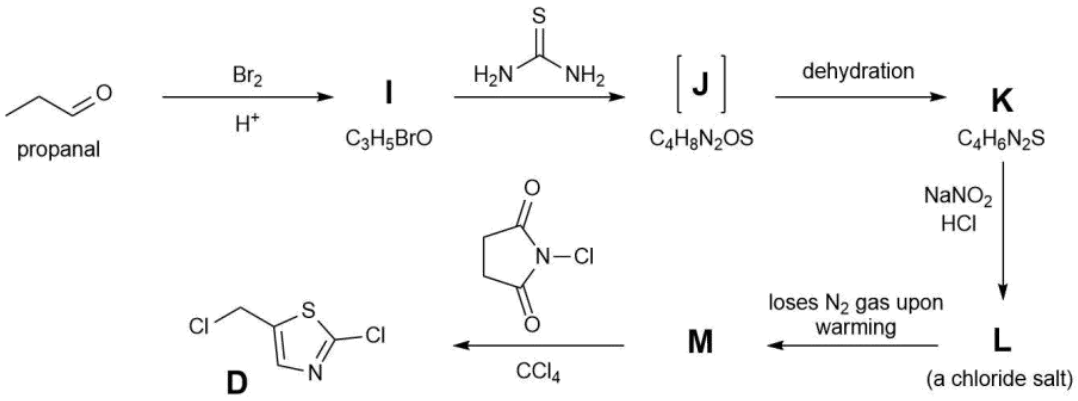


(d) Draw the electrophile that reacts with guanidine to form **E**, clearly indicating its shape.

(e) Draw the structures of **E**, **F**, **G** and **H**. You only need to draw one tautomer for each compound.

Question 5.(source,UKChO,2019,4f-4g)

In an alternative synthesis of thiamethoxam, compound **D** can also be synthesised from propanal.



(f) Draw the structures of **I** and intermediate **J**.

Intermediate **J** undergoes dehydration to form **K**. There are three possible tautomers of **K**.

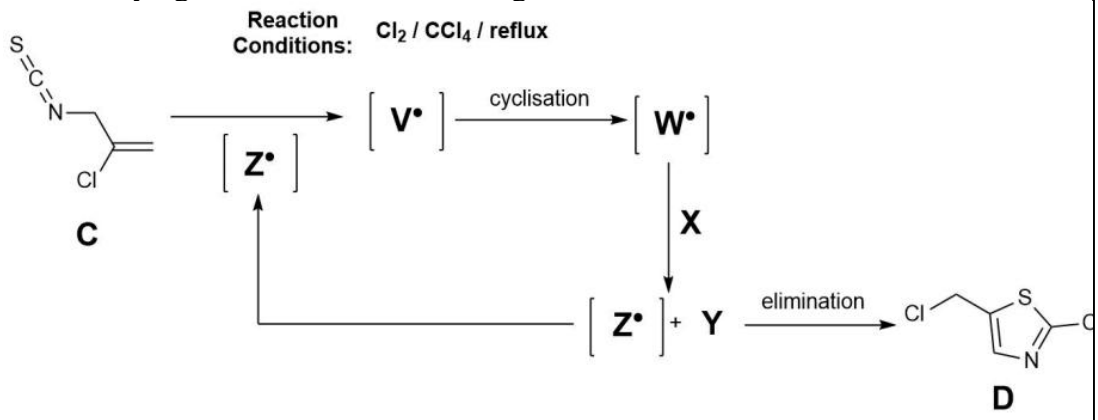
However, as one tautomer is aromatic (as it has six electrons in a ring like benzene), this tautomer is far lower in energy than the other two. Hence, at equilibrium this lowest energy tautomer predominates.

(g) Draw the structure of the lowest energy tautomer of **K** (showing the electrons as double bonds rather than as a circle).

(h) Draw the structures of **L** and **M**.

(source,UKChO,2019,4i-4j)

The conversion of **C** to **D** occurs via a free radical chain reaction, followed by an elimination. The chain-carrying radical Z* adds to the thiocyanate in **C** to give radical intermediate V*. Intermediate V* undergoes cyclisation to give radical intermediate W*, which reacts with reagent **X** to form **Y** and regenerate the chain-carrying radical Z*. **Y** then undergoes an elimination to form **D**.



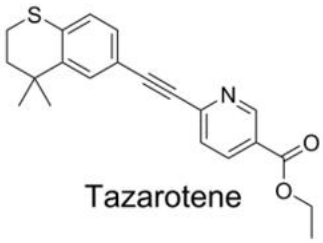
(i) Draw the structures of radical intermediates $V^{\bullet}$ and $W^{\bullet}$, and intermediate **Y**.

(j) Identify reagent **X** and chain-carrying radical $Z^{\bullet}$.

Question 6.(source,UKChO,2014,3a-3b)

This question is about spot cream

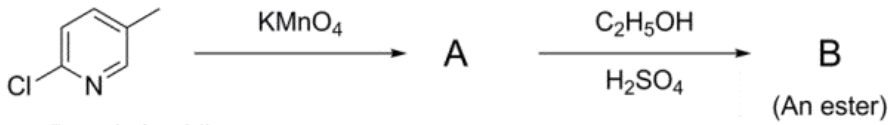
The drug tazarotene (sold under the trade names of Zorac® or Tazorac®) can be prescribed as a cream that can be applied to the skin to help to treat acne and certain other skin conditions. It is commonly sold as a 0.05% cream by mass.



Tazarotene

(a) The molar mass of tazarotene is 351.46 g mol^{-1}. Assuming that tazarotene cream has a density of 0.90 g cm^{-3}, calculate the concentration of tazarotene in the cream in mol dm^{-3}.

The synthesis of tazarotene is shown below. Not all of the reaction by-products are shown. The synthesis begins with the conversion of 2-chloro-5-methylpyridine to Ester **B**.

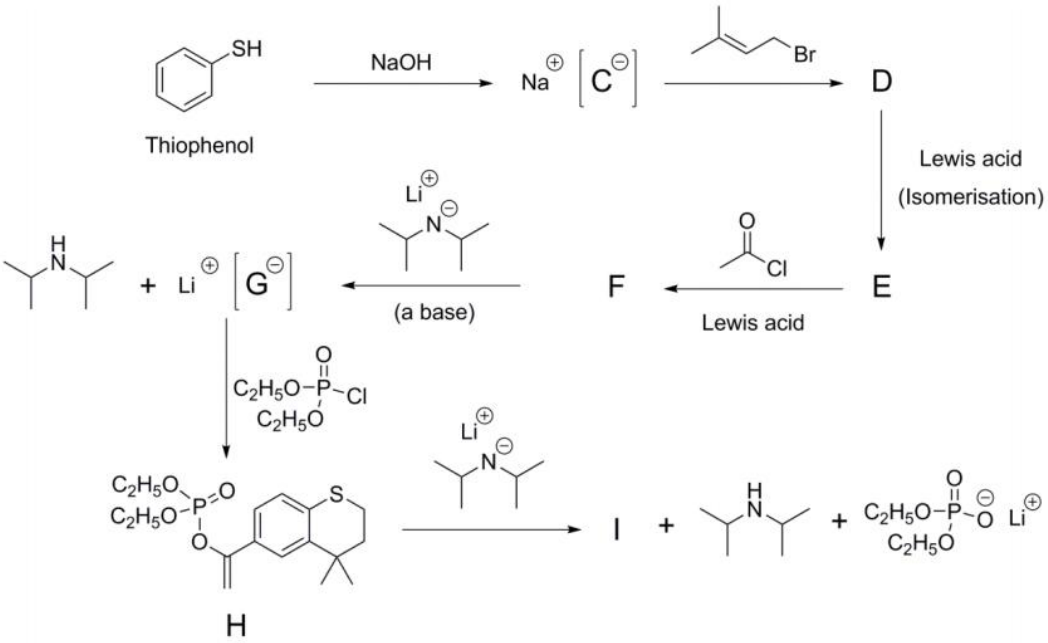


2-Chloro-5-methylpyridine

(b) Draw the structure of Compound **A** and Ester **B**.

(source,UKChO, 2014, 3c-3e)

The second part of the synthesis begins with thiophenol, which is converted into Compound **I** by a number of steps.



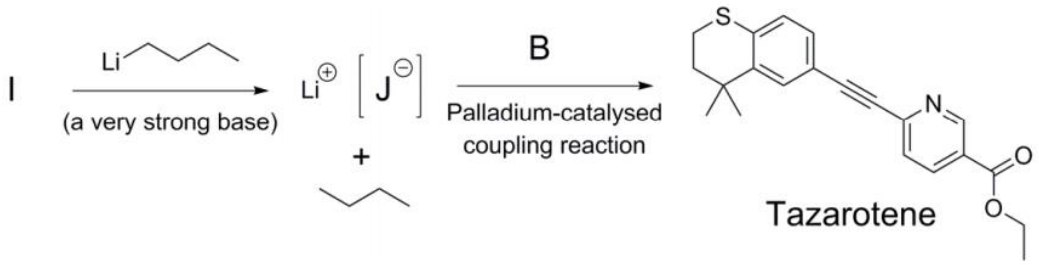
(c) Draw the structures of Compounds D, E, F and I, and anions C^- and G^-.

(d) How would you classify the reaction of Compound H into Compound I?

Circle one of the following answers in the answer booklet.

Oxidation **Reduction** **Addition** **Elimination** **Substitution**

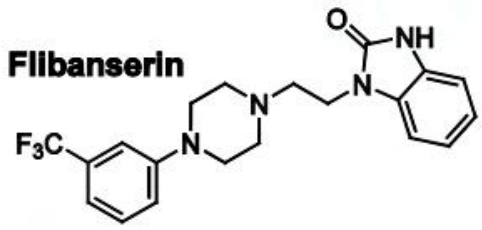
Finally, Compound **I** is treated with a very strong base to form anion **J**.
Anion **J** can be reacted with Compound **B** to form tazarotene.



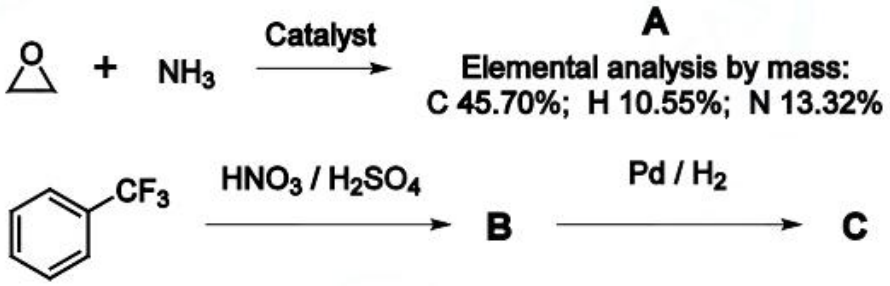
(e) Suggest a structure for Anion **J**.

Question 7.(*source,UKChO, 2016, 4a-4b*)

In 2015, the drug Addyi (chemical name Flibanserin) made the news by becoming the first drug to be approved for the treatment of female hypoactive sexual desire disorder. The structure of Addyi is shown below.



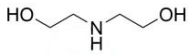
In making this molecule, two precursor molecules **A** and **C** are first synthesised as shown in the scheme below.



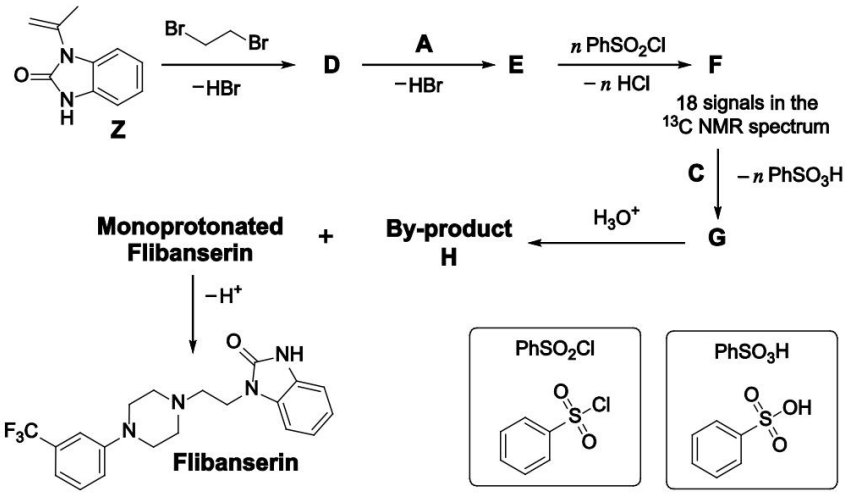
(a) Calculate the empirical formula of **A**.

(b) Draw the structures of Compounds **A**, **B** and **C**.

UKChO, 2016, 4c,4d

Conclusion of the question(b)-the structure of A is 

The remainder of the synthesis starts with Compound **Z** and is shown below. In this scheme all reactions are balanced.



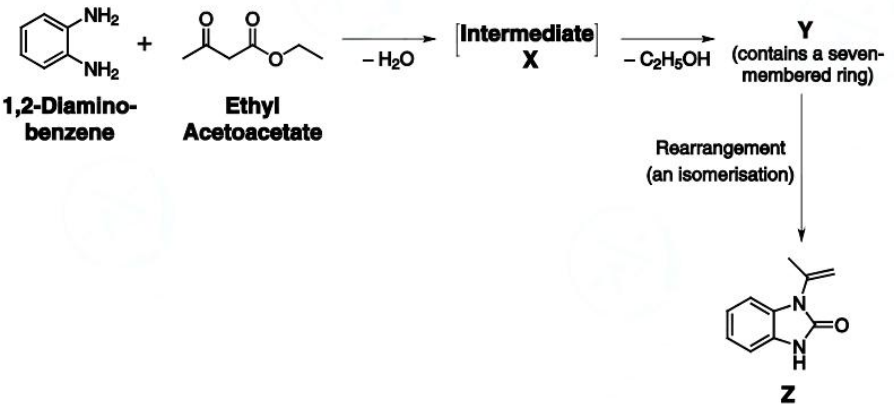
(c) Draw the structures of Compounds **D**, **E**, **F** and **G** and the By-Product **H**.

(d) Flibanserin is formed initially as its monoprotonated salt. On the structure of Flibanserin in your answer booklet, circle the atom that is protonated.

(Source,UKChO, 2016, 4e)

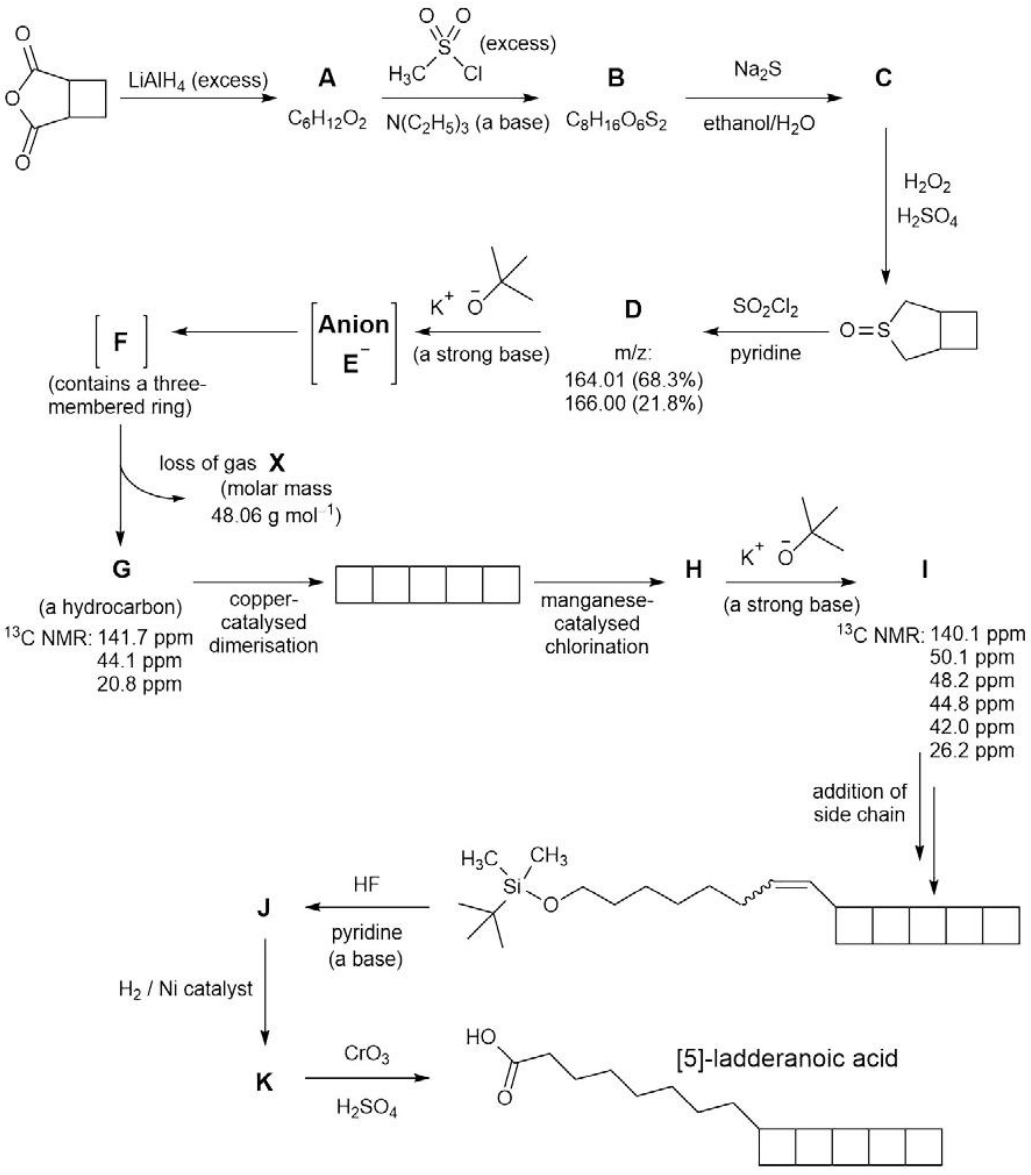
Compound **Z** itself is synthesised from 1,2-diaminobenzene and ethyl acetoacetate. The synthesis is shown in the scheme below, where all reactions are balanced.

(e) Draw the structures of Intermediate **X** and Compound **Y**.



Question 8.(Source,UKChO, 2020, 6d)

To further understand the lipids found in these bacteria, a research group synthesised [5]-ladderanoic acid – a key component of such lipids. The synthesis is shown below. Not all by-products are shown.



(d) Draw the structures of compounds **A** – **K** and by-product **X**. No stereochemistry is required in any structure.

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