ChemFactsheet

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Changing the Carbon Skeleton

Introduction

The ability to change the carbon skeleton by increasing or decreasing the carbon chain length in organic synthesis is a critical consideration. For example, in the pharmaceutical industry the final product needs to be obtained from simple, available and inexpensive starting reagents. Such reagents rarely possess the required number of carbon atoms and so modifications to the carbon backbone are an essential part of the synthetic route. Converting one functional group to another functional group can be a relatively easy thing to achieve, but changing the carbon backbone from the starting materials requires a more specific approach.

In less specific situations, we encounter the alteration of the carbon skeleton in processes applied in the petroleum industry. This usually involves one of three key processes:

1) **Cracking** – This involves breaking a larger molecule down into smaller and more useful ones. For example, decane can be split into propene and heptane according to the equation below.

$$C_{10}H_{22} \rightarrow C_3H_6 + C_7H_{16}$$

The cracking process is achieved using high heat (steam cracking), or catalysts (catalytic cracking). Typically, catalysts include crystalline zeolite, which are complex aluminosilicates.

2) **Isomerisation** – This involves the rearrangement of a molecule to create a new hydrocarbon, typically one with greater branching. For example, the straight chain hydrocarbon butane is converted to the branched hydrocarbon 2-methylpropane. Branched hydrocarbons are used as additives in petrol.

$$C_4H_{10} \rightarrow CH_3CH(CH_3)CH_3$$

The isomerisation process is carried out at high temperatures and in the presence of catalysts, usually a combination of fine platinum powder on a zeolite base.

3) **Reforming** – This involves the conversion of straight-chained hydrocarbons into cyclic hydrocarbons, resulting in the release of hydrogen gas. This is described as an elimination reaction. Reforming can also be used to produce important aromatic compounds from straight chained hydrocarbons, for example, in the reforming of hexane to benzene, and heptane to methylbenzene. Note that reforming is a significant contributor to the industrial production of hydrogen.

$$C_6H_{14} \rightarrow C_6H_6 + 4H_2$$

$$C_7H_{16} \rightarrow C_6H_5CH_3 + 4H_2$$

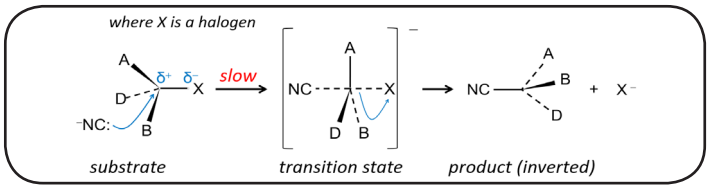
Such reforming reactions are catalyst driven, often using platinum and aluminium oxide.

Lengthening the Carbon Chain

Nucleophilic Substitution with Cyanide

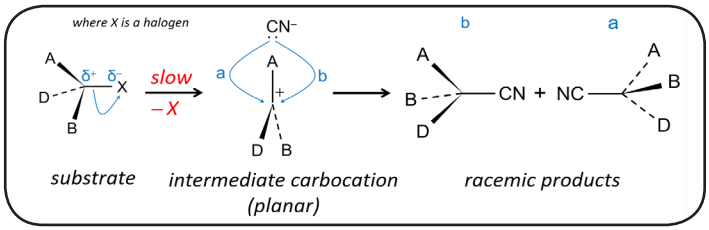
The reaction of nucleophiles with halogen containing organic compounds is one with a well-understood mechanism that generically resembles one of two routes. For the reaction with primary halogenoalkanes we observe an S_N2 mechanism, where the rate determining step involves two components, thus:

Figure 1



For a tertiary halogenoalkane, we observe a S_N1 mechanism, where the rate determining step involves just one component, thus:

Figure 2



The nucleophiles used in these reactions are many and various but they have one thing in common. They must be able to donate a lone pair of electrons to a relatively positive active site on a molecule to create a covalent bond. Such nucleophiles include; hydroxide ions, OH^-, used to produce alcohols, and ammonia, NH_3, used to produce amines.

Arguably the most important of these reactions is that of the cyanide ion with a halogenoalkane. The cyanide ions are introduced into the reaction mixture as either the potassium or sodium salt. An ethanol solvent is used. In this reaction, the cyanide ions act as a nucleophile and the product is a nitrile. For example, potassium cyanide, dissolved in ethanol, is added to 1-chloropropane and heated under reflux, this reaction will yield butanonitrile according to the equation below:

$$CH_3CH_2CH_2Cl + CN^- \rightarrow CH_3CH_2CH_2CN + Cl^-$$

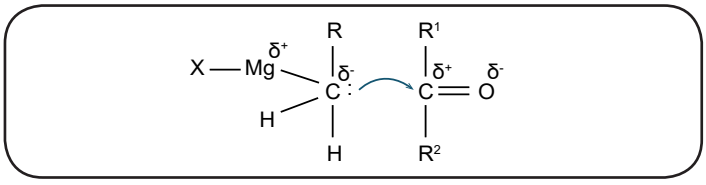
In this reaction step, a three carbon-chain becomes a four carbon-chain.

Note: *An important note about the use of solvents.*
The use of ethanol as the solvent is critical in this reaction. Using water as a solvent creates a problem. The hydrolysis reaction of cyanide ions produces an abundance of hydroxide ions in solution according to this equation:
$CN^- + H_2O \rightarrow HCN + OH^-$
The aqueous hydroxide ions act as nucleophiles themselves and are therefore in competition, preventing the desired attack by the cyanide ions.

Grignard Reagents

In 1912, the French chemist Victor Grignard was awarded the Nobel Prize in Chemistry for developing Grignard reagents. These are useful in organic synthesis and are used to extend the length of the carbon chain. They have the general formula R-Mg-X, where R is an alkyl or aryl group of some description, and X is a halogen atom, typically chlorine or bromine. The polarity of the C–Mg bond forms a powerful nucleophilic carbon, which attacks the partially positive carbonyl carbon, introducing the incoming R-group from the Grignard reagent. The variation of the R–group makes for a versatile reagent, with different products obtainable.

Figure 3



Like other organometallic compounds, Grignard's are highly reactive species, especially in the presence of water. This means Grignard reagents are created 'in situ', i.e. in the reaction mixture. The reaction of a Grignard reagent with water is not a desired one. At room temperature an alkane is produced, although this is not a preferred method for preparing alkanes.

$$CH_3MgBr + H_2O \rightarrow CH_4 + Mg(OH)Br$$

This reaction illustrates why it is necessary to carry out Grignard reactions in dry ether (i.e. ethoxyethane) instead of water. Note that the above reaction can be used to produce isotopically labelled hydrocarbons, replacing hydrogen atoms with deuterium by using D_2O in the reaction.

The first stage of any reaction involving Grignard's involves preparing the Grignard reagent. This is completed by adding magnesium turnings to a halogenoalkane (not containing fluorine), in dry ether and with a trace of iodine. The formation reaction is very exothermic and requires cooling. An example is the conversion of bromomethane to a Grignard reagent:

$$CH_3Br + Mg \rightarrow CH_3MgBr$$

Once made, the Grignard reagent can then react in several ways.

a) With gaseous methanal followed by dilute HCl at room temperature to produce a primary alcohol with an extended carbon-chain.

$$CH_3MgBr + HCHO \rightarrow CH_3CH_2OMgBr$$

$$CH_3CH_2OMgBr + H_2O \rightarrow CH_3CH_2OH + Mg(OH)Br$$

In this example, the methyl (R–group) in the Grignard reagent bonds to the single carbonyl carbon on methanal, introducing an extra carbon atom. The reaction completes forming a two-carbon primary alcohol. Different primary alcohols are obtained by starting with a different Grignard reagent.

b) With any aldehyde, other than methanal, followed by dilute HCl at room temperature to produce a secondary alcohol, e.g. ethanal.

$$CH_3MgBr + CH_3CHO \rightarrow (CH_3)_2CHOMgBr$$

$$(CH_3)_2CHOMgBr + H_2O \rightarrow (CH_3)_2CHOH + Mg(OH)Br$$

In this example, the Grignard reagent bonds to the single carbonyl carbon, adding the R–group and extending the carbon-chain to form 2-propanol, a secondary alcohol.

c) With any ketone followed by dilute HCl at room temperature to produce a tertiary alcohol, e.g. propanone

$$CH_3MgBr + CH_3COCH_3 \rightarrow (CH_3)_3COMgBr$$

$$(CH_3)_3COMgBr + H_2O \rightarrow (CH_3)_3COH + Mg(OH)Br$$

Once again, the R–group in the Grignard reagent bonds to the single carbonyl carbon, increasing the carbon-chain length of the carbonyl molecule. In this example the carbon-chain is increased from three carbon atoms to four, producing the tertiary alcohol, 2-methyl propane-2-ol.

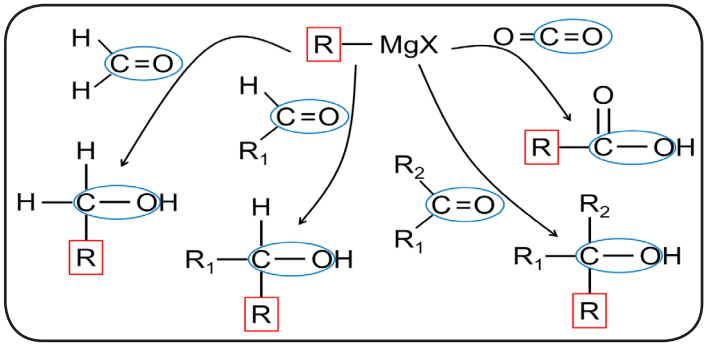
d) With solid carbon dioxide, followed by dilute HCl at -70°C, and then raised to room temperature to produce a carboxylic acid

$$CH_3MgBr + CO_2 \rightarrow CH_3COOMgBr$$

$$CH_3COOMgBr + HCl \rightarrow CH_3COOH + MgBrCl$$

Here, carbon dioxide introduces an additional carbon atom, converting the single carbon atom Grignard to a two-carbon carboxylic acid.

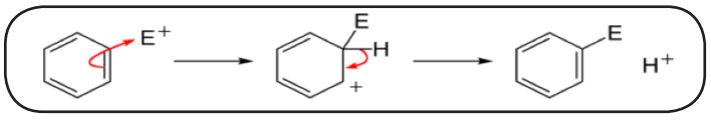
Figure 4 Summary of Grignard reactions



Friedel-Crafts Reaction

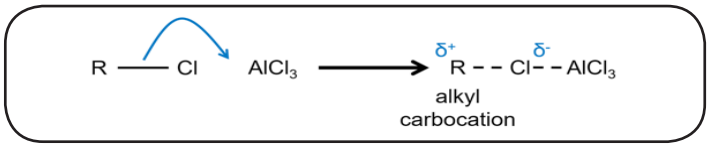
The reaction was developed in 1877, by James Crafts and Charles Friedel, and involves attaching substituents to an aromatic ring. This is achieved through either alkylation or acylation and is catalysed using a halogen carrier, for example, aluminium chloride or iron(III) chloride. This creates an electrophile that attacks the aromatic benzene ring. The electrophilic attack of the benzene ring is another well-understood mechanism. The generic version is shown below, where 'E' is the incoming electrophile.

Figure 5



If an alkyl or acyl carbocation is generated, it acts as an electrophile and the carbon chain of this incoming alkyl or acyl group can be added to the ring. This yields a product with additional carbon atoms. In these reactions, an electron deficient halogen carrier, e.g. $AlCl_3$, is used as a catalyst to generate the carbocation electrophile:

Figure 6

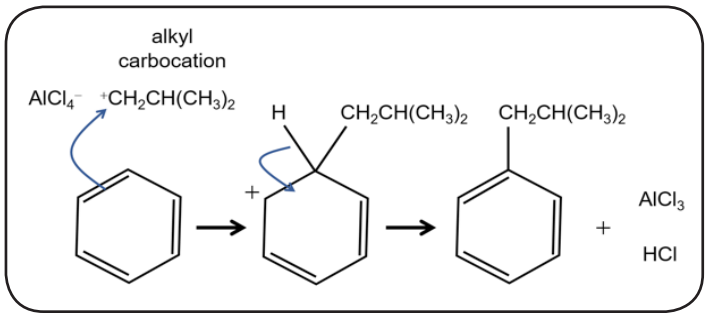


An acyl carbocation can be generated in the same way by using a carbonyl compound, rather than R-Cl as the reagent. For example:

Figure 7

The equation below describes how 2-methyl-1-chloropropane combines with the halogen carrier aluminium chloride to attach 2-methylpropyl to benzene via a Friedel-Crafts reaction. The same mechanism can be applied for the attack of an acyl chloride. In both cases the carbocation acts as the electrophile. Note that the aluminium chloride catalyst is regenerated in the reaction.

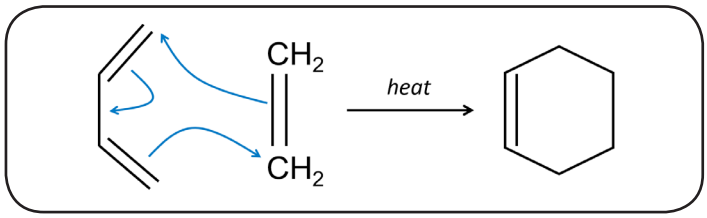
Figure 8



Diels-Alder Reaction

This is another reaction that won a Nobel Prize in Chemistry for its inventors. The Diels-Alder reaction, created by Otto Diels and Kurt Alder in 1928, involves the combination of a 1,3-diene with an alkene (referred to as a dienophile) to produce a single, cyclohexene ring. In its simplest form, shown below, we see that the reaction takes a four-membered carbon chain and a two-membered carbon chain and combines them into a six-membered ring, hence lengthening the chain and creating a cyclic structure.

Figure 9



In organic synthesis, six-membered carbon ring systems are very common. Most alkenes and dienophiles can be brought together in the Diels-Alder reaction to form them. This demonstrates the reaction is an incredibly important synthetic tool.

Shortening the Carbon Chain

Hoffman Degradation

Although the Diels-Alder reaction can be reversed to split a cyclohexene ring into a diene and dienophile, it's not considered as a generic method for shortening a carbon-chain. A reaction used to shorten a carbon-chain is the Hofmann degradation. The reaction was first published in 1881 by August Wilhelm von Hofmann. Hofmann was a student of Justus von Liebig (Liebig condenser), and a mentor of Fritz Haber (Haber synthesis of ammonia). He became an accomplished chemist and was a pioneer of using molecular models in his teaching. The Hofmann degradation converts an amide into an amine by removing the carbonyl group, i.e. lessening the carbon-chain by one carbon atom. An example of the reaction involves the conversion of ethanamide to methanamine. The reaction mixture is heated to 70°C with bromine and concentrated potassium hydroxide as the reagents.

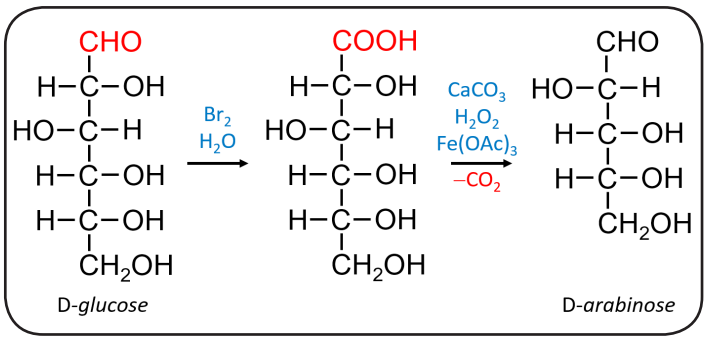
$$CH_3CONH_2 + Br_2 + 4KOH \rightarrow CH_3NH_2 + K_2CO_3 + 2KBr + 2H_2O$$

In this instance, a two-membered carbon chain is converted to a compound containing a single carbon atom. The carbonyl group (C=O) is eliminated, thus converting a primary amide to the primary amine. The reaction works for different R-groups, including both aliphatic and aromatic compounds.

Ruff Degradation

A reaction developed around same time as the Hofmann degradation, by another German chemist, Otto Ruff, which also removes a carbon atom from a chain. The Ruff degradation is a more specific reaction and is used to shorten the carbon chain length of aldose, a sugar, by one carbon atom. The reaction relies upon the oxidation of the aldehyde group to a carboxylic acid and the subsequent removal of carbon dioxide.

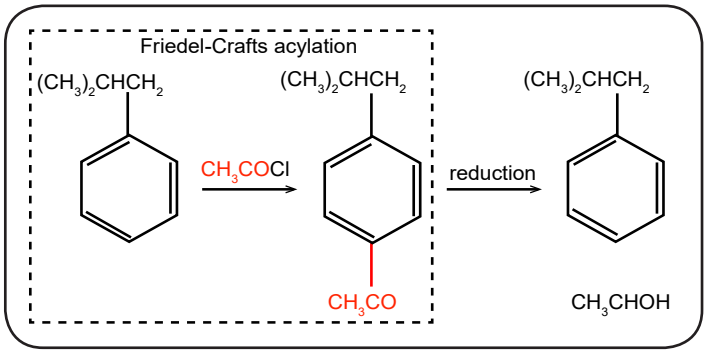
Figure 10



The Synthesis of Ibuprofen

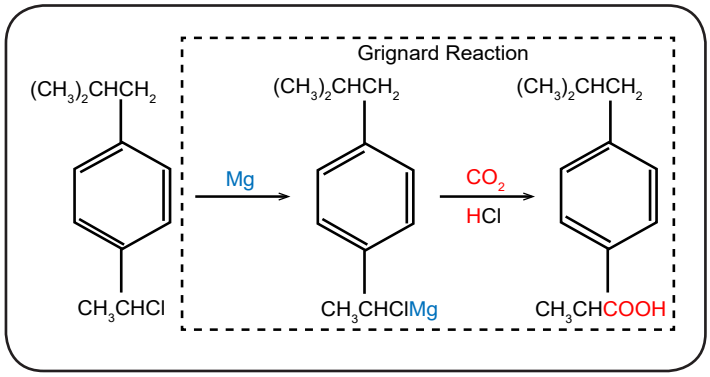
The manufacture of this popular pain reliever requires several steps using different reagents to change the carbon skeleton and convert functional groups. The first step is the Friedel-Crafts acylation of 2-methylpropylbenzene, $(CH_3)_2CHCH_2C_6H_5$, by adding an ethanoyl group to the aromatic ring. This is followed by reduction of the ketone to an alcohol, and then halogenation, for example, with a chlorine atom substituting the hydroxyl group.

Figure 11



The final steps involve preparing a Grignard reagent and the completion of the carboxylic group. Note the further addition to the carbon-chain.

Figure 12



Questions

1) Describe how the alcohol 2-methylpropan-2-ol can be prepared using a Grignard reagent.
2) Outline a preparation of methylamine from ethanoyl chloride.

Answers

1) 2-methylpropan-2-ol is a tertiary alcohol so the reaction can be carried out with a Grignard in conjunction with a ketone.

   The ketone can contain three carbons, so the Grignard would need only one, for example:

   $$CH_3MgBr + (CH_3)_2C = O \rightarrow \text{2-methylpropan-2-ol}$$

2) Convert ethanoyl chloride to ethanamide via a reaction with ammonia and cooling.

   $$CH_3COCl + NH_3 \rightarrow CH_3CONH_2 + HCl$$

   Perform a Hofmann degradation with bromine and potassium hydroxide.

   $$CH_3CONH_2 + Br_2 + 4KOH \rightarrow CH_3NH_2 + K_2CO_3 + 2KBr + 2H_2O$$

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