11 SYNTHESIS OF MATERIALS

Chemistry has many aspects; but there are three general regions: the study of structures of materials, the study of reactions of materials, and the synthesis of materials. Previously, it was generally thought that synthesis, compared with structure and reactions, was more empirical and devoid of rigid theory. As our understanding of structures and reactions has advanced, however, synthesis has also gradually become theoretically grounded and systematized.

In this chapter we shall glimpse of the state at the art of modern synthesis. This will help you to recognize the significant role of synthesis in modern chemistry.

11.1 Establishment of the concept of synthesis

One of the main purposes of chemistry is to create necessary materials, namely, **synthesis**. From the advent of alchemy, this purpose was the most important object to attain. It was not easy to attain this purpose. Alchemy contributed to the birth of modern chemistry by its improving experimental techniques and devices. Such techniques as refluxing and distillation were the achievements of their efforts. To alchemists, however, these achievements were not what they sought. They never achieved their ultimate purpose of synthesizing gold though many of them had reported success.

The reason for their failure is obvious. Their work was based on a false hypothesis: the theory of Aristotle’s four elements (Ch. 1.1). Their target, gold, is an element, but they regarded gold as a kind of compound and thought that the compound they sought might be obtained by mixing four elements in an appropriate proportion.

The modern concept of synthesis could not be conceived until the atomic theory was established and the structure of molecules was elucidated in terms of atomic theory. Such a situation was finally realized at the middle of the 19th century. The valence theory of Kekulé and Couper was proposed around 1858. Not all chemists at that time were, however, ready to use Kekulé’s valence theory, which was characterized, by the use of “a bond” between atoms. The concept of valence was vague, and some chemists thought that this was a mere measure of the proportion of various types of atoms in the molecule.

The Russian chemist Aleksandr Mikhailovich Butlerov (1828-1886) eagerly supported the Kekulé-Couper theory, and declared that one and only one chemical formula was to correspond to one compound and that the atoms in the molecule were bonded to each other in accordance with the valence theory, denying the prevailing assumption that atoms were randomly assembled in the molecule. According to him, the valence was not a mere measure of the proportion of atoms in the molecule; it defined the pattern of bonding between atoms in the molecule. He first used the term **chemical structure** in 1861.

According to his theory, there should exist isomers when two or more than two ways of bonding atoms are possible for one rational formula. Around that time, the German chemist Adolph Wilhelm Hermann Kolbe (1818-1884) successfully synthesized isopropyl alcohol $(CH_3)_2CHOH$ and Butlerov himself synthesized *t*-butyl alcohol $(CH_3)_3COH$. These successes proved the existence of secondary and tertiary alcohols and in turn established the concept of chemical structure.

The French chemist Michel Eugène Chevreul (1786-1889), a contemporary, found that fats were compounds of fatty acids (aliphatic carboxylic acids) and glycerin, and that fat-like materials were obtained by the reaction of any fatty acid with glycerin. Berthelot wrote a textbook “*Organic Chemistry*” in 1860 in which he used the term “synthesis”. He declared that in principle any organic compound could be synthesized from carbon, hydrogen, oxygen and nitrogen.

Thus, the basic philosophy of synthetic chemistry was established in the middle of the 19th century. The practice of synthesis was by no means easy. In 1856, an eighteen years old English boy William Henry Perkin (1838-1907), an assistant to August Wilhelm von Hofmann (1818-1892) who was then in London because he had been asked to construct a system for chemistry education in England, attempted to synthesize quinine. Quinine was known as the specific drug for malaria. At that time, no method for synthesizing such a complex compound as quinine from simple organic compounds was available.

Perkin had an idea that quinine might be obtained by the oxidation of allyltoluidine, which had a rational formula similar to that of quinine. As a matter of fact that was utterly impossible, and indeed his attempt to synthesize quinine failed. Instead, however, he obtained a wonderful dye, later named Mauve or Mauvein, which became the first artificial dye put to practical use. This accidental success prospered the chemical industry greatly. However, the difficulty of organic synthesis remained unsolved.

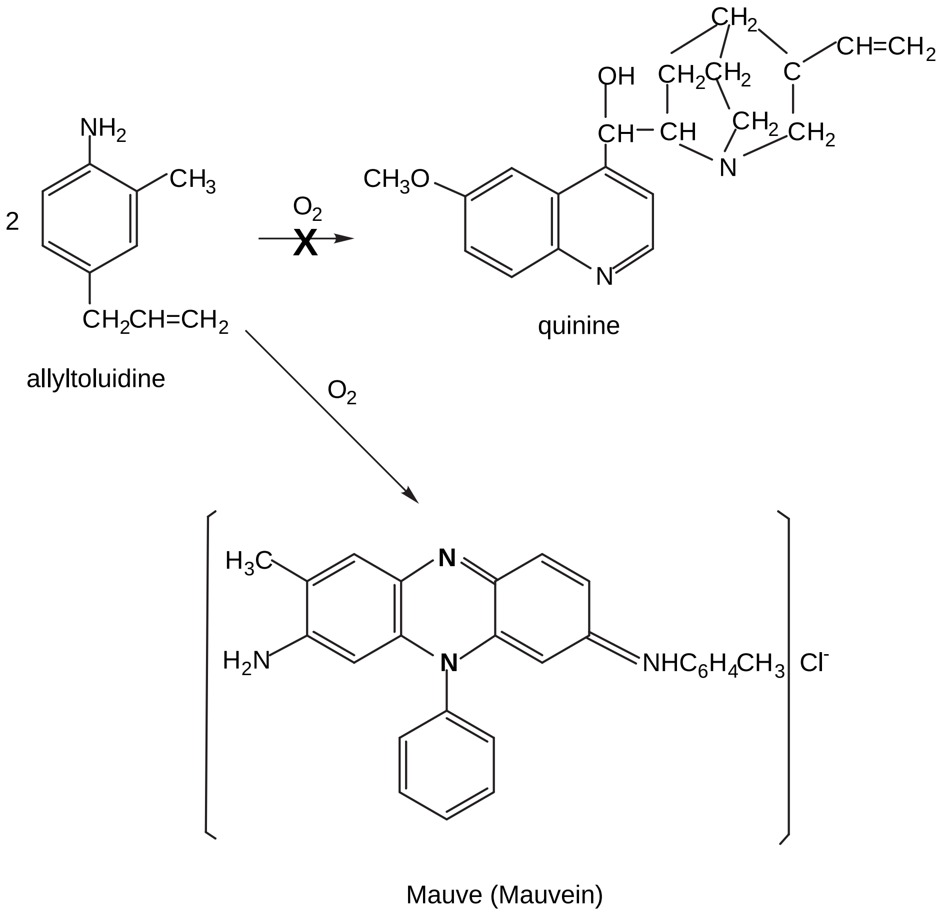


Fig. 11.1 What great luck! By the oxidation of allyltoluidine Perkin obtained, not the quinine he sought, but the first artificial dye, Mauve.

It was 88 years later in 1944 that the American Chemist Robert Burns Woodward (1917-1979) was able to synthesize quinine by a systematic approach.

12.2 Synthesis of inorganic industrial materials

Since the structures of inorganic compounds are generally simpler than these of organic compounds, the synthesis of inorganic compounds had been reasonably advanced from the very beginning of modern chemistry. Many enterprisers and inventors extensively explored the syntheses of some useful compounds. In other words, the syntheses of useful inorganic compounds were actively promoted before their structures or the mechanisms of their reactions were not yet clarified. Some representative examples are given below.

(a) Sodium carbonate Na_2CO_3

Throughout the history of industrial chemistry, the supply of sodium carbonate Na_2CO_3, soda, was the most important issue. Soda was an important raw material not only for common daily needs (like soap) but also for more sophisticated industrial products (like glass).

In ancient times soda was obtained from natural sources, and potassium carbonate K_2CO_3, which also was used for soap, was obtained form wood ash. After the Industrial Revolution, the demand for soap increased and consequently new synthetic methods were eagerly sought. It was recognized that soda and salt (NaCl) contained a same element, sodium, and this discovery prompted attempts to develop a process of producing soda from salt. In the beginning of the 19^{th} century, a process was developed in which a mixture of sodium sulfate, the by-product of the production of hydrogen chloride (to be used for the production of bleaching powder), charcoal and iron were ignited. The yield was, however, low and was not suitable for large-scale production.

The French inventor Nicolas Leblanc (1742-1806) applied for a contest, held by *Académie des Sciences*, for the effective production of soda from salt. The essence of his process was the use of limestone (calcium carbonate $CaCO_3$) instead of iron.

The outline of Leblanc's process

$$Na_2SO_4 + 2C \rightarrow Na_2S + 2CO_2 \qquad (11.1)$$

$$Na_2S + CaCO_3 \rightarrow Na_2CO_3 + CaS \qquad (11.2)$$

$$2NaCl + H_2SO_4 \rightarrow Na_2SO_4 + 2HCl \qquad (11.3)$$

Leblanc's process could provide soda of better quality as compared with the products by previous methods. However, this process produced a quantity of by-products such as sulfuric acid, hydrogen chloride, calcium sulfide and hydrogen sulfide. The factories became the target of social criticism even then. Improvements of Leblanc's process were highly desirable particularly in view of the reuse of by-products, which could certainly reduce the cost of production.

One century after the proposal of Leblanc's process, the Belgian inventor Ernest Solvay (1838-1922) proposed Solvay's process (ammonia-soda process), which was much advanced in chemical and technological aspects. It was already known in early 19^{th} century that soda could be produced from salt and ammonium carbonate $(NH_4)_2CO_3$. Solvay had experiences on machines and could design the process of production not only from chemical viewpoint but also from the viewpoint of chemical engineering. He succeeded to industrialize the process in 1863.

The greatest advantage of Solvay's process was the use of a tower reactor instead of a tank reactor. Salt water which dissolved ammonia was poured from the top of the tower and carbon dioxide was blown into the tower from the bottom so that the product could continuously be recovered without stopping the reaction. Solvay's system substantially reduced the cost, and consequently the new process took the place of Leblanc's process.

The outline of Solvay's process

Main reaction

$$NaCl + NH_3 + CO_2 + H_2O \rightarrow NaHCO_3 + NH_4Cl \qquad (11.4)$$

$$2NaHCO_3 \rightarrow Na_2CO_3 + CO_2 + H_2O \qquad (11.5)$$

Circulation of ammonia

$$2NH_4Cl + CaO \rightarrow 2NH_3 + CaCl_2 + H_2O \qquad (11.6)$$

Formation of carbon dioxide CO_2 and calcium oxide CaO

$$CaCO_3 \rightarrow CaO+CO_2 \qquad (11.7)$$

The only by-product of Solvay's process was calcium chloride, and ammonia and carbon dioxide were circulated and reused. In production of soda from salt, the crucial point was the disposal of chlorine. In Leblanc's process, chlorine was discharged as hydrogen chloride gas but in Solvay's process, chlorine was disposed as solid, harmless calcium chloride. By virtue of its effectiveness and efficiency, Solvay's process was regarded an example of chemical-industrial process.

(b) Sulfuric acid

As early as in the latter half of the 16th century, the German chemist Andreas Libavius (1540?-1616) described a process to obtain sulfuric acid H_2SO_4 by burning sulfur in wet air.

$$S + O2 \rightarrow SO_2 \quad (11.8)$$

$$2SO_2+O_2 \rightarrow 2SO_3 \quad (11.9)$$

Glauber, the first chemical engineer, invented in the middle of the 17th century, a process to obtain hydrochloric acid by heating a mixture of salt and sulfuric acid. His hydrochloric acid had higher concentration as compared with the ones previously obtained.

$$2NaCl+H_2SO_4 \rightarrow Na_2SO_4+2HCl \quad (11.10)$$

This reaction is described in high school chemistry textbooks currently in use. Glauber advertised sodium sulfate as a medicine with marvelous effects and obtained a fortune by selling the salt.

A more practical process was introduced in which sulfur was heated with saltpeter (potassium nitrate KNO_3). At first the burning was conducted in a large glass jar which contained some water. The sulfuric acid formed was dissolved in the water. Though the 2nd step of the process ($SO_2 \rightarrow SO_3$) was slow and endothermic, in this process the oxides of nitrogen seemed to act as a catalyst to promote the reaction.

As the demand for sulfuric acid increased especially because of Leblanc's process which required sulfuric acid in quantity, a new device, chamber process using a chamber lined with lead sheets instead of glass-jar was introduced which made a large scale production possible. A large-scale production of sulfuric acid was necessarily accompanied with a discharge of a quantity of nitrogen oxides. Such was even then a serious environmental hazard which could not be disregarded.

A few improved processes were introduced using Gay-Lussac and Glover towers. The latter was widely used since nitrogen oxides could be reused and the yield of nitrate was high with Glover tower.

The idea of using some catalysts in the production of sulfuric acid, or rather, in the oxidation of sulfur dioxide was known since *ca*. 1830. Platinum catalyst was proved effective but very expensive and hence was not widely used. After half a century when the demand of sulfuric acid increased very much, the idea of using catalysts revived. After the problem of catalyst poison was solved, the process using platinum catalyst, *i.e.,* the contact process, became the main process of production of sulfuric acid. The contact process is used even now though the catalyst used today is not of platinum but a mixture including vanadium. oxide V_2O_5.

(c) Ammonia and nitric acid

Nitrates (salts of nitric acid) had a large demand for the row material of gunpowder from olden times. The supply was limited, however, and naturally occurring saltpeter (KNO_3) was the sole resource available. In the 19th century when the scale of wars became enormous, the demand for nitrates became proportionally large, and the naturally occurring saltpeter could not meet that demand.

In addition, nitrates were necessary for the row material of artificial fertilizers. It was the later half of the 19th century when the German chemist Justus von Liebig (1803-1873) proved the effectiveness and importance of artificial fertilizers. The problem which prevented wider use of artificial fertilizers was the high price, especially, of nitrogen fertilizers.

At the end of the 19th century, the English physicist William Crookes (1832-1919) predicted that the increase of the amount of food produced could not catch up with the increase of population and the world would run into the catastrophe.

Such circumstances prompted scientists to investigate the artificial fixation of nitrogen, or to find a process to convert nitrogen which inexhaustibly existed in air into some compounds which man could use. It was absolutely necessary to carry out the fixation in a large scale. Thus, the experiment should start in a laboratory scale to end in a factory scale.

The fixation of nitrogen was successfully achieved by he German chemist Fritz Haber (1868-1934) and the German engineer, employed by BASF, Carl Bosch (1874-1940). The equation for the Haber-Bosch process is very simple, but technically there are several difficulties. The process was elaborated so that this exothermic and equilibrium reaction would proceed to the right side smoothly.

$$N_2 + 3H_2 \rightarrow 2NH_3 + 22.1\ \mathrm{kcal} \qquad (11.11)$$

In practice, several modifications were made. For instance, the molar ratio of nitrogen : hydrogen is not 1 :3, but 1 :3.3. The reaction condition was chosen as 300°C at 500 atm. Hydrogen was used in excess at high pressure so that the equilibrium would shift to the right. Since the reaction is exothermic, the reaction should better be carried out at lower temperature in view of Le Chatelier’s principle. On the other hand, the rate of reaction tends to be very slow at lower temperature. Hence the temperature is kept rather high (*i.e.*, to the extent that the decomposition of NH_3 will not take place.) Catalyst made of iron is now extensively used.

The Haber-Bosch process became famous as the first example in which the theory of equilibrium was applied to the practical production. On one hand, the fixation of nitrogen by the Haber-Bosch process brought a great benefit to man as for the fertilizers. On the other hand, this also meant that the row material for gunpowder could be obtained inexhaustibly.

The modern process of production of nitric acid HNO_3 is the air oxidation of ammonia. In this process, ammonia is mixed with excess air, and the mixture is heated to high temperature in the presence of platinum catalyst to be converted to nitrogen oxide NO, which is further oxidized in air to nitrogen dioxide NO_2. Nitrogen dioxide is reacted with water to give nitric acid. This method was developed by Ostwald, who established the chemistry of catalyst, and is called Ostwald’ process. The process is represented by the following equations.

The outline of Ostwald’s process

$$4NH_3 + 5O_2 \rightarrow 4NO + 6H_2O \qquad (11.12)$$

$$2NO+O_2 \rightarrow 2NO_2 \qquad (11.13)$$

$$3NO_2+H_2O \rightarrow 2HNO_3+NO \qquad (11.14)$$

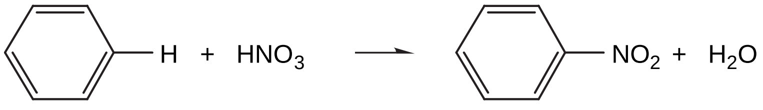
11.3 Organic Synthesis

Compared with the synthesis of inorganic compounds, that of organic compounds was much more difficult. The birth of organic chemistry was attributed to the synthesis of urea $CO(NH_2)_2$ (a typical organic compound) by heating ammonium cyanate (an inorganic compound) by the German chemist Friedrich Wöhler (1800-1882). Only recently it became possible to design and synthesize desired compounds.

Reactions used in organic synthesis can be classified into two groups;

1. formation of carbon-carbon bonds
2. Conversion of functional groups

Most of the reactions you learned at high school are the conversion of functional groups as shown below.



(11.15)

$$CH_3COOH + C_2H_5OH \longrightarrow CH_3COOH + H_2O \qquad (11.16)$$

To organic synthesis the formation of C-C bonds and the conversion of functional groups are something like two wheels of a vehicle. It is not appropriate to ask which is more important. A variety of reactions for C-C bond formation have been reported. Based on the driving force of the reactions, these can roughly be classified into three types; aldolol condensation, the Grignard reaction and the Diels-Alder reaction. Here the last two will be explained.

(a) The Grignard reaction

The Grignard reaction was discovered by the French chemist Francois Auguste Victor Grignard (1871-1935) in 1901. The initial stage of the reaction is the preparation of methylmagnesium iodide, a Grignard reagent, from the reaction between alkyl halide (methyl iodide in the example below) and magnesium in dry diethyl ether.

$$CH_3I + Mg \rightarrow CH_3MgI \qquad (11.17)$$
methyl iodide methylmagnesium iodide

You must notice that magnesium is directly bonded to carbon. Such compounds as the Grignard reagents in which C-metal bonds are included are called the **organometallic compound**. The C-metal bonds are labile and leave carbanions such as CH_3^- after the cleavage of the bond takes place. The anions of carbon like CH_3^- tend to attack positively charged carbon atoms.

It is well known that carbon atoms of an aldehyde group or of a keto group bear partial positive charge due to electronegative carbon atoms. These carbons are attacked by carbanions such as CH_3^- to give adducts which will give secondary alcohols from aldehydes or tertiary alcohols from ketones, respectively, after hydrolysis.

$$C_6H_5CHO + CH_3MgI \rightarrow C_6H_5CH(CH_3)OMgI \qquad (11.18)$$
benzaldehyde

$$C_6H_5CH(CH_3)OMgI + HCl \rightarrow C_6H_5CH(CH_3)OH + MgClI \qquad (11.19)$$
1-phenylethanol

$$C_6H_5COC_2H_5 + CH_3MgI \rightarrow C_6H_5CH(CH_3)(C_2H_5)\ OMgI \qquad (11.20)$$
propiophenone

$$C_6H_5CH(CH_3)(C_2H_5)OMgI + HCl \rightarrow C_6H_5CH(CH_3)(C_2H_5)OH + MgClI \qquad (11.21)$$
2-phenyl-2-butanol

The Grignard reaction is an example of the reactions of organometallic compounds. Since many kinds of aldehydes and ketones are easily available, a variety of organic compounds can be prepared with the aid of the Grignard reaction.

Sample exercise 11.1 The Grignard reaction

In the text, a combination of $C_6H_5COC_2H_5$ and CH_3MgI was used for synthesizing 2-phenyl-2-butanol $C_6H_5CH(CH_3)(C_2H_5)OH$. Indicate other combinations that allow to prepare the same compound.

Answer

Three types of alkyl groups are included in the final product. These alkyl groups may be a part of any starting material. Thus, in addition to the combination of $C_6H_5COC_2H_5$ and CH_3MgI, two other combinations are acceptable.

(1) acetophenone $C_6H_5COCH_3$ and ethylmagnesium iodide C_2H_5MgI
(2) ethylmethylketone $CH_3COC_2H_5$ and phenylmagnesium iodide C_6H_5MgI

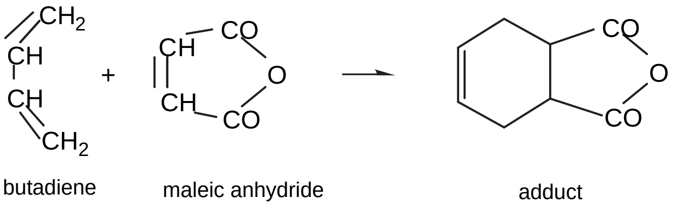
(b) The Diels-Alder reaction

The driving force of the Grignard reaction is the attraction between two different electric charge on two carbon atoms. Such reactions are called the **ionic reaction** or the **polar reaction**. There are other types of organic reactions. One is the **radical reaction**, the driving force of which is the reactive radical species generated during the reaction. If a phenyl radical is generated, it will attack a benzene molecule to give biphenyl.

$$\underset{\text{phenyl radical}}{C_6H_5\bullet} + C_6H_6 \rightarrow \underset{\text{biphenyl}}{C_6H_5\text{-}\ C_6H_5} + H\bullet \qquad (11.22)$$

Most of organic reactions are classified into either the ionic reaction or the radical reaction. In the first half of the 20th century, it gradually turned out, however, there is another group of reactions which cannot be classified into none of these two. The representative one is the Diels-Alder reaction discovered in 1928 by two German chemists Otto Paul Hermann Diels (1876-1954) and Kurt Alder (1902-1958).

In this reaction an electrically neutral butadiene reacts with maleic anhydride which is also electrically neutral to give a cyclic product.



(11.23)

Interestingly, it turned out that there are many examples of this type of reactions: a diene (compounds with two double bonds) and an alkene activated by such as carbonyl of cyano groups smoothly react to afford cyclic products. It must be added that no reaction takes place between two butadienes or two maleic anhydride.

In 1965, two American chemists, Woodward and Roald Hoffmann (1935-) explained that this type of reactions are not the ionic nor the radical reactions, but the reactions are the result of the overlap of molecular orbitals of two reactants. This interpretation allowed to elucidate the mechanism of various reactions hitherto unknown.

According to them, a favorable interaction will take place when one reactant (*e.g.*, butadiene) has four π electrons and the other reactant (*e.g.*, maleic anhydride) two π electrons to afford a cyclic product. It was shown that the highest occupied molecular orbitals (**HOMO**) and the lowest unoccupied molecular orbitals (**LUMO**) govern the course of the reaction. At the same time Ken-ichi Fukui (1918-1999) named these orbitals as the **frontier orbital**.

The significance of the reactions quoted in this chapter will be acknowledged by the fact that Grignard, Diels, Adler, Woodward, Hoffmann and Fukui are all Nobel Laureates.

Coffee break

The climax of organic synthesis

From the beginning of organic chemistry, organic synthesis may be regarded as the core of organic chemistry. Organic synthesis may be said to have enjoyed its climax around the middle of the 20th century when Woodward was most active. Woodward achieved the syntheses of such compounds as quinine (1944), strychnine (1954), chlorophyll (1960) and cephalosporin (1966). Meanwhile he received the Nobel Prize in 1965.

Robert Burns Woodward (1017-1979)

The highlight of Woodward's achievement is the successful synthesis of vitamin B_{12} which was done with a cooperation with the Swiss chemist Albert Eschenmoser (1925-). The two groups were responsible to synthesize a half of this complex molecule. After the target species were synthesized, these were combined to afford vitamin B_{12}.

(c) Asymmetric synthesis

As you have learned in Ch. 4, many naturally occurring organic compounds, such as amino acids, sugars and steroids, have the asymmetric carbon atom. Quinine, which was introduced in this chapter also has asymmetric carbon atoms. The asymmetric carbon atom plays the key role in the physiological activity of all these compounds. It must be added that in most cases only one of the enantiomeric pair is useful for man. In this regards, whether man can achieve the asymmetric synthesis, an art of selectively synthesizing one of the enantiomeric pair, is a crucial issue.

In the successful examples of the asymmetric synthesis, compounds with the asymmetric carbon atom, such as terpenes, amino acids and sugars, is chosen as one of the reactant. The asymmetric carbon atom will make a site which might favor the formation of one of the enantiomer. The selective formation of one isomer might be affected by the steric effect. In certain cases, the rate of reaction might be different between two stereoisomers. In other cases, the equilibrium between two product isomers might be shifted to one side. The selective synthesis of necessary isomer will be the most important and most extensively investigated topic of organic chemistry in the 21st century.

There is also more difficult approach in which no auxiliary compounds with an asymmetric carbon atom is used. If this type of asymmetric synthesis is realized, we shall be able to say that chemistry can now mimic nature!

Exercise

11.1 Solvay's process

Answer the following questions on Solvay's process

(1) Write the series of equations from the starting materials to sodium carbonate.

(2) Give the name(s) of gas(es) which is (are) repeatedly used in this process.
(3) Calculate the weight of sodium carbonate obtained from 1 ton of sodium chloride.

11.1 Answer

(1) See the text.
(2) CO_2, NH_3
(3) 0.906 ton

11.2 The Grignard reaction

You are expected to synthesize an alcohol $C_3H_7C(CH_3)(C_2H_5)OH$ by means of the Grignard reaction. Suggest all possible combinations of organic compounds (an aldehyde or a ketone) and Grignard reagents (obtainable from bromides).

11.2Answer

$CH_3COC_2H_5$ and C_3H_7MgBr, $C_2H_5COC_3H_7$ and CH_3MgBr, $CH_3COC_3H_7$ and C_2H_5MgBr