

Hemos invitado al autor de la sección *PARA QUITARLE EL POLVO* "La química en la historia, para la enseñanza" durante los últimos trece números a participar en la sección *DE ANIVERSARIO* con una contribución de la misma categoría que las anteriores, dedicada al tema de *QUÍMICA DE FRONTERA*, como todavía puede catalogarse el trabajo de Grignard por el que obtuvo el premio Nobel en 1912.

François Auguste Victor Grignard

Jaime Wisniak*

Resumen

A Victor Grignard (1871-1935) le debemos el descubrimiento de la reacción que lleva su nombre, relacionada con la síntesis de derivados organometálicos que pueden ser usados como intermediarios en la preparación sencilla de una amplia gama de compuestos químicos, en particular, alcoholes secundarios y terciarios. El paso de Grignard de una carrera en matemáticas a otra en química fue el resultado de una serie de eventos burocráticos que lo llevaron a recibir el Premio Nobel de Química en 1912.

Abstract

To Victor Grignard (1871-1935) we owe the discovery of the reaction that carries his name, involving the synthesis of organomagnesium derivatives that can be used as intermediates for the easy preparation of a wide range of chemicals, in particular, secondary and tertiary alcohols. Grignard's switch to a career in chemistry instead of mathematics was the result of a series of fortuitous bureaucratic events that led to his receiving the Nobel Prize for Chemistry in 1912.

Life and career (Bram *et al.*, 1997; Courtot, 1936; Cologne, 1950)

François Auguste Victor Grignard (Figure 1) was born at Cherbourg, May 6, 1871, the son of Marie Hébert and Théophile Henri Grignard, a foreman and sail maker at the local marine arsenal. Victor attended the lycée at Cherbourg from where he graduated with honors in 1887. At that time the city of Paris offered scholarships to brilliant graduates from the secondary schools in the provinces, to prepare for the entrance examinations to one of her universities. The Cherbourg lycée had received a promise that Grignard would be awarded one of those scholarships in order to prepare for the entrance examinations to the *École Normale Supérieure* in Paris. Unfortunately, because of the expenses involved in the preparation of the 1889 World Exposition

(that would see the inauguration of the Eiffel Tower) no scholarships were offered at the time of Grignard's graduation from high school. Whoever took this decision, could have hardly guessed the tremendous impact it would have in the development of organic chemistry. Grignard was left with no alternative but to register at the *École Normale Secondaire Spéciale* at Cluny, an institution that had been established in 1866 as a training



Figure 1. Victor Grignard.

school for teachers of modern secondary education, for those who wanted to become businessmen, farmers, or study classical subjects as preparation for the liberal professions. One problem followed another because this *École* was closed in 1891, as a result of a reform of the secondary education law. As a consequence, Grignard and all other students were transferred to the University of Lyon to complete their studies. In 1892, after failing in his exams for the licentiate in mathematics, he enrolled in the army for his military service and then returned to Lyon to complete his studies of mathematics (*License ès-Sciences Mathématiques*) in 1894.

Louis Rousset, a classmate from Cluny, influenced Grignard to overcome his dislike for chemistry and to accept a position (December, 1894) as *préparateur adjoint* in general chemistry at the Faculty of Sciences of Lyon, working for Louis Bouveault (1864-1909). Grignard had a very poor opinion of chemistry, he believed that compared to mathematics, chemistry was a minor science, totally empirical and requiring a memorizing effort that was beyond his aptitudes. Association with Bouveault made him change his mind; through his master he understood the logical of chemistry and the way to look for the crucial experience that would demonstrate the point in question. In 1895 he was promoted to *préparateur* and began a long association with Philippe Antoine Barbier (1848-1922), a former student of Marcelin Berthelot (1827-1907) and the head of the department of

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Figure 2. Swedish stamp honoring Grignard's Nobel Prize.

chemistry. In 1889 Barbier had successfully realized the conversion of an unsaturated acetone into the corresponding ternary alcohol using methyl iodide and magnesium instead of zinc as called for by the Saytzeff method.

After obtaining his degree of *Licence ès-Sciences Physiques* Grignard was promoted to *chef des travaux pratiques* in 1898, replacing his close friend Rousset who had passed away very young. In the same year he published his first scientific paper in collaboration with Barbier (Grignard and Barbier, 1898). This paper was followed by another one describing a method for the synthesis of hydrocarbons having simultaneously double and triple bonds and about hydrocarbons having three conjugated double bonds (Grignard, 1899).

He now started looking for a doctoral thesis topic; first he got first interested in the subject of enzymes but Barbier convinced him who switch to the study of the new reaction he had discovered. In 1901 he submitted his brilliant thesis on chemical synthesis using organomagnesium compounds (Grignard, 1901a) and was awarded the degree of *Docteur ès Sciences* by the Faculty of Sciences of Lyon.

Grignard was appointed *Maitre de Conférences* at Besançon in 1905, and after one year there he returned to Lyon to occupy a similar position until 1908 when he was promoted to *Professeur Adjoint de Chimie Générale*. In 1909 he was appointed Head of the Department of Organic Chemistry at the University of Nancy, replacing Edmond Blaise (1872-1939), and promoted to Professor of Organic Chemistry in 1910. That year he married Augustine Marie Boulant, and had two sons with her, Robert Paindestre and Roger, born in 1911.

In 1919 he returned to Lyon to succeed his former professor, Barbier, as Professor of General Chemistry. In 1921 he was also appointed *Directeur de l'École de Chimie Industrielle*, became a member of the University Council, and in 1919 he became Dean of the Faculty of Sciences until his death on December 13, 1935, following a severe surgical operation.

Grignard was very prolific, publishing over 170 papers and books. A complete listing of his works appears in a paper by Courtot (1936).

Honors

Grignard received many honors for his contributions to chemistry. He was made Chevalier de la Legion d'Honneur

in 1912, Officier in 1920, and Commandeur in 1923. He was awarded the Cahours Prize of the Institute of France in 1901 and 1902; the Berthelot Medal in 1902; the Prix Jecker in 1905; the Lavoisier Medal of the Société Chimique de France in 1912; the Gold Medal of the Société de Chimie Industrielle in 1931; and the Gold Honor Medal of Hygiène Public in 1933. In November 1912 he was awarded the Nobel Prize for Chemistry for his 1900 discovery of the role of organomagnesium compounds in synthesis (Figure 2); together with Paul Sabatier (1854-1941), for his discoveries in catalytic hydrogenation of organic compounds by means of finely divided metals.

Grignard occupied many public and scientific positions in France, for example, Officier de l'Instruction Publique (1908); member of the Commission de Nomenclature de la Chimie Organique (1912 and 1921); member of Commission des Etudes et Expériences Chimiques de Guerre (1919); member of the Conseil Départemental de Hygiène de Rhône (1922); and member of the Comité Scientifique des Poudres et Explosives (1930). At the University of Lyon he was professor of general chemistry, director of the school of industrial chemistry, and Dean of the Faculty of Sciences at Lyon. He was also professor of organic chemistry at the University of Nancy

Grignard was nominated member of many scientific societies in France and abroad, among them, foreign member of the Royal Swedish Academy of Science (1909); corresponding fellow of the Société des Sciences Naturelles de Cherbourg (1913); corresponding member (1913) and full member (1926) of the Institut de France; honorary fellow of the American Chemical Society (1917); honorary fellow of the Mellon Institute, Pittsburgh (1918); honorary fellow of the Chemists Club of New York (1918); honorary fellow of the Royal Society of London (1920); and honorary fellow of the Société Chimique de Belgique (1920). He was honorary professor of the University of Nancy (1931) and held honorary doctorates of the universities of Louvain (1927) and Brussels (1930).

The Grignard reaction

In 1875 the Russian chemists G. Wagner (1849-1903) and Alexander Saytzeff's (1841-1910) had shown that it was possible to synthesize tertiary alcohols by the reaction between an organozinc compound with ketones (different from methyl ketones), a reaction that resulted in condensation products and elimination of water (Wagner and Saytzeff, 1875). Edward Frankland (1825-1899) (Frankland, 1848-1849) and James Alfred Wanklyn (Wanklyn, 1861) had easily prepared solutions of zinc alkyls by heating zinc with alkyl iodides in sealed tubes, in the presence of anhydrous ether. In contrast to the free zinc alkyls, these solutions did not catch

fire on contact with air and yet they had the characteristic reactivity. Wanklyn had observed that the reaction of zinc and methyl iodide was greatly facilitated by the presence of anhydrous ether but it was necessary to perform it in a sealed tube. Frankland had found that heating at 100°C for eight hours a mixture of zinc, methyl iodide, and anhydrous ether produced a volatile product having the same properties as methylzinc and fitting the formula $Zn(CH_3)_2 \cdot O(C_2H_5)_2$. In his paper Frankland described the laborious technique he developed to prepare organic zinc derivatives, of which the prototype was methyl zinc, $Zn(CH_3)_2$. His procedure was very limited and for alkyl radicals up to amyl the yield was very low. All the compounds were highly flammable in contact with air, were dangerous to handle, and reacted very slowly with certain chemical functions, again with very low yields. Further improvements in the preparation techniques did not solve these problems and the organozinc derivatives were accessible only to skilful and careful experimenters.

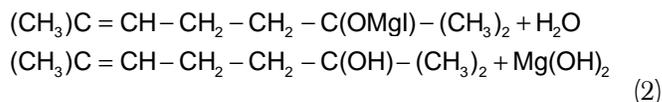
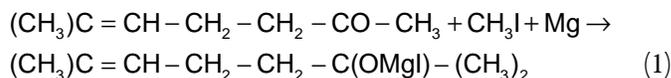
Following the pioneering work of Frankland, W. Hallwachs and A. Schafarik (Hallwachs and Schafarik, 1859) in Göttingen and Auguste Cahours (1813-1891) (Cahours, 1860) in Paris tried to react alkyl iodides with metals other than zinc. Cahours, for example, reported that methyl iodide and ethyl iodide yielded with magnesium flammable liquids that reacted with water to give methane and ethane.

These difficulties led, towards the end of the nineteenth century, to some attempts to use other metals, magnesium in particular, which at that time was used only for pyrotechnics and photography illumination.

The reactivity of methyl and ethyl iodide with magnesium had also been observed, though the magnesium available at that time was not very pure. However, organomagnesium compounds were not studied closely until 1891 on, when Lothar Meyer (1830-1895) had several of his students carry out research on this topic. The first of these was Löhr, who prepared dimethyl-, diethyl, and dipropyl magnesium by heating magnesium filings with the alkyl iodide in a closed tube, or better by heating the mercury alkyl iodide with magnesium amalgam in a closed evacuated tube. He found that the products were solid, unstable non-volatile materials, which spontaneously ignited in the air or in dry carbon dioxide, and were insoluble in neutral solvents, excepting a mixture of dry ether and benzene (Löhr, 1891). The series of researches done by Meyer and his students revealed the strong reactivity of organomagnesium compounds, but they were discarded as possible reagents for chemical synthesis because they were hard to prepare and had unfavorable properties (slight solubility in inert solvents, inflammability in air and carbon dioxide).

In 1897, while Barbier was working on the synthesis of methylheptenone, a natural product, he realized that he

needed to prepare 2,6-dimethylhept-5-ene-2-ol. He had at his disposition 6-methylhept-5-ene-2-one and Barbier thought of using it as the starting material for his synthesis. To do so he modified Saytzeff's method by replacing the zinc with magnesium and conducting the reaction in anhydrous ether. He first covered the magnesium filings with an ether solution of the ketone and then gradually added methyl iodide. He noticed that when one-third of the iodide had been added a violent exothermal reaction took place, which he proceeded to control by cooling. Subsequent hydrolysis with ice and dilute acid yielded the required alcohol. In 1899 Barbier reported his results in a short note presented to the *Académie des Sciences* (Barbier, 1899) and suggested that the reaction went through an intermediate compound between the ketone and magnesium, which was then decomposed into the alcohol by the water:



Barbier also reported that his synthesis could be applied to other related reactions, but that the results and yields were unpredictable.

Coupling the unfavorable findings of Barbier's investigations with Frankland and Wanklyn's observations regarding the need for the presence of anhydrous ether, led Grignard to suspect that replacement of zinc by magnesium might eliminate some of the operating difficulties encountered by Frankland. His reasoning was based on magnesium being more electropositive and more reactive than zinc a fact that would lead perhaps to an easier reaction with higher yield. Experimental work proved this to be true: magnesium in the presence of anhydrous ether reacted easily with halogenated alkyls at room temperature and the reaction yielded organomagnesium derivatives, which were completely soluble in ether (Grignard, 1901b),

Grignard performed some exploratory experiments of the reaction between magnesium and isobutyl iodide and quickly became convinced that it took place spontaneously in absolute ether at room temperature and under ordinary pressure, and that no preliminary heating of the magnesium with the alkyl halide was necessary. He recognized the exceptional reactivity of these ether solutions. He found that although methyl iodide reacted very slowly with magnesium filings, addition of a small amount of anhydrous ether resulted in such a strong reaction that it was necessary to cool

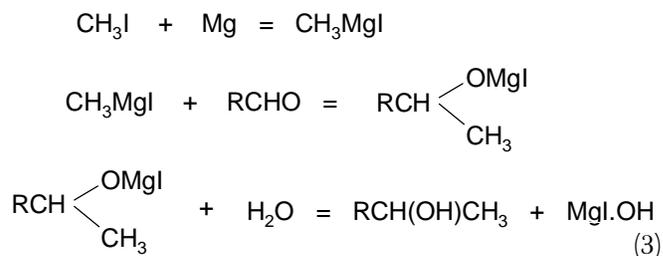
it by addition of an excess of ether. Under these conditions magnesium dissolved very fast and the final product was a very fluid liquid, slightly colored, and with no significant solid deposit (Grignard reported that the magnesium he used was about 99.3% weight pure and contained traces of iron). Analysis of the solution indicated that it contained exactly one atom of magnesium per molecule of methyl iodide; but more important, that it was not necessary to evaporate the ether, addition of the stoichiometric amount (one molecule) of ketone or aldehyde (for example benzaldehyde) produced a very vigorous reaction. The final product treated with acid and water produced the pertinent secondary or tertiary alcohol with about 70% yield.

Grignard also studied the solid material left after eliminating the ether. The methyl iodide of magnesium decomposed brusquely at about 255°C releasing white fumes and abundant violet vapors of iodine. The small amount of distillate produced was a viscous liquid stained with iodine. The behavior of ethyl bromide magnesium was similar, except that at 300°C the decomposition was very violent, producing ethane, ethylene, magnesium bromide, and magnesium.

He submitted his first findings in a paper to the Académie des Sciences, which was presented by Henri Moissan (1852-1907; 1906 Nobel Prize for Chemistry) (Wisniak, 2002). In this paper Grignard proceeded from Barbier's communication and reported that in his study of the eventual advantages of his method he had discovered a number of organo compounds of magnesium, which enabled him to modify the Saytzeff method considerably: "Au cours de ces recherches, j'ai decouvert une série de combinaisons organométalliques du magnésium qui m'ont permis de modifier notablement la methode de Saytzeff-Wagner, au grand profit de la rapidité et de la regularité de l'operation et, en général, du rendement obtenu" (During these researches I have discovered a series of magnesium organometallic combinations that have allowed me to modify substantially the Saytzeff-Wagner method to the great profit of the speed and the regularity of operation and, in general, of the yield obtained).

Grignard upheld that his organomagnesium compounds corresponded to the formula RMgI or RMgBr , where R was a fatty or aromatic alcoholic residue, and that the reactions he had realized could be explained by the following mechanism:

He stated that in this way he had prepared a certain number of secondary and tertiary alcohols, some of which were previously known, but he had repeated their synthesis in order to assume himself of the general validity of his method. He reported that the results were generally very good with aliphatic alkyl halides, but much less so with



benzyl bromide because of the abundant formation of dibenzyl. He further stated that when using unsaturated aldehydes, or ketones, in which the double bond was adjacent to the functional group, the resulting alcohol was unstable; it dehydrated when distilled, even under reduced pressure, so that only a diethylenic hydrocarbon could be isolated.

In the following year Grignard published seven papers on the subject and submitted his doctoral thesis. After the first paper, Moissan had urged the young chemist to present his thesis in Paris, even though it would be only half finished, but Grignard preferred to dedicate it to the university where his discovery had been made. Accordingly, he received the degree *Docteur ès Sciences Physiques* at Lyon, in July 18, 1901, when he was 30 years old. The examining committee graded the thesis *Mention très honorable*. As quoted by Courtot (1936), Georges Urbain (1872-1938) said that Grignard's debut in chemistry was undoubtedly unique in the history of chemistry; already in his second paper he announced one of the most important discoveries that had taken place in organic chemistry.

Grignard's thesis listed twenty-nine new compounds prepared by his method, including isoamyrfurfurylcarbinol, phenylisobutyl carbinol (phene-1-methyl-3-butanol-1), dimethylphenyl carbinol (phene-2-methyl-2-ethanol), and dimethylbenzyl carbinol (phene-1-methyl-2-propanol-2). He described a considerable number of mixed organomagnesium compounds, remarking that they were present as ethers in an ethered medium, and noted the general applicability of the compounds for synthesis. In particular, his thesis described the synthesis of carboxylic acids by the action of carbon dioxide on the ether solution of the organomagnesium halide; the preparation of secondary alcohols from aldehydes or formic esters, the synthesis of tertiary alcohols from ketones, carboxylic acid esters, and acid halides or anhydrides, as well as the preparation of unsaturated hydrocarbons from tertiary alcohols.

Some of the conclusions he listed were:

- (a) Alkyl bromides or iodides (RX) reacted very easily with magnesium in the presence of anhydrous ethers, to yield organometallic compounds of the general formula RMgX .

- (b) The organomagnesium compounds were totally soluble in ether, could be used in solution and could easily replace the similar organozinc derivatives, with many operational advantages.
- (c) The compounds decomposed easily with water yielding the pertinent hydrocarbons.
- (d) In certain reactions the new compounds were similar to the pertinent organosodium species; they fixed carbon dioxide and, in the presence of water, produced the corresponding acids.
- (e) The organomagnesium compounds could be used to prepare symmetric secondary or tertiary alcohols.

The Grignard method was now firmly established. Grignard concluded that the mixed organomagnesium compounds would be a valuable tool for the synthesis of mono-basic acids, alcohols, and hydrocarbons and that they were superior to the organozinc compounds with respect to the ease of handling, wider applicability, and improved yields.

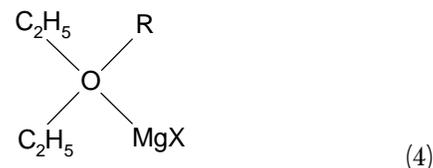
The significance of Grignard's fundamental discovery was immediately appreciated in France. The Académie des Sciences awarded him its most prestigious prizes: the Cahour prize in 1901 and 1902, and the Berthelot Medal in 1902.

During the period 1901 to 1911 Grignard devoted all his efforts to improve his initial findings. He was fortunate to have the assistance of Louis Tissier, who at that time was *Maitre de Conférence de Chimie* at Lyon, and who would, eventually enter politics and become senator of the Republic. Together they published a large number of papers dealing with the synthesis of primary and tertiary alcohols by the action of trioxymethylene or acid chlorides and anhydrides on organomagnesium compounds. They found that phosgene in the presence of acid chlorides reacted in a similar fashion as ketones, and that for the synthesis of ketones from acid chlorides it was better to use mixed organozinc compounds instead of the ones having magnesium. The latter finding led Edmond Blaise (1872-1939), who held the chair of Organic Chemistry at Nancy, to develop his elegant procedure for the preparation of aromatic organozinc mixtures by the double decomposition of organomagnesium compounds and zinc chloride (Courtot, 1936).

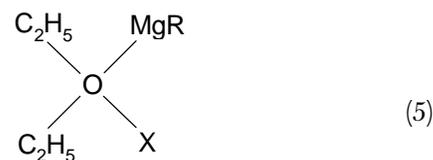
Later on Grignard studied the action of organomagnesium compounds on keto ethers and found that the reaction was normal for positions different from β . Since the keto group is more reactive than the group carboxyalcohol, slow addition of magnesium to the keto ether led the CO group to react first and yield ether-salt alcohols. Eventually, the procedure yielded bitertiary glycols, and constituted a new path for asymmetric syntheses.

The first discussion on the composition of the etherates

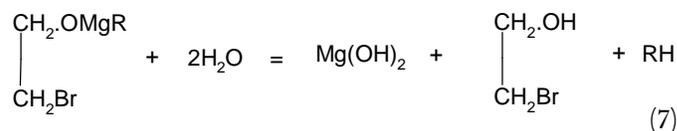
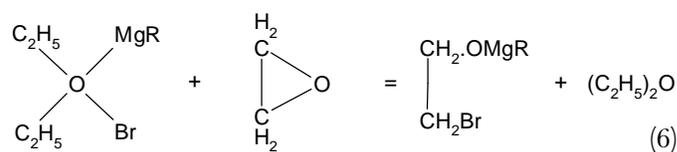
of the organomagnesium halides took place between Grignard and Blaise. Both accepted the mixed formula RMgX , not free but attached to one or more ether molecules. According to Grignard the correct structure was



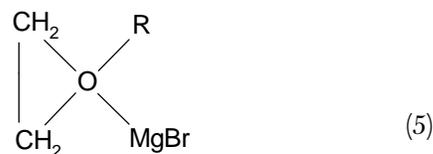
while Blaise advocated the structure proposed by Adolph von Baeyer (1835-1917) and Villiger on the basis of their oxonium theory (Baeyer and Villiger, 1902):



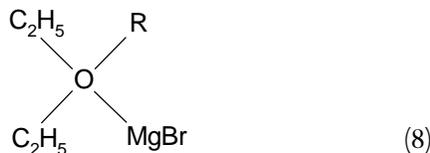
In 1902 Blaise had reacted organomagnesium compounds with ethylene oxide and obtained a small amount of the alcohol $\text{R}(\text{CH}_2)_2\text{OH}$ and a significant amount of ethylene bromhydrin, $\text{CH}_2\text{OH}-\text{CH}_2\text{Br}$. He considered that his results ratified the Baeyer and Villiger structure so that the reactions taking place were:



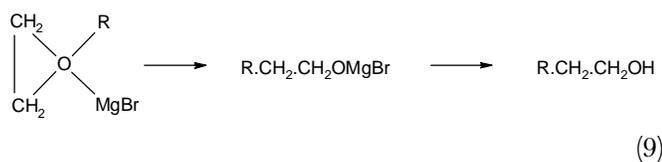
On the other hand, when Grignard had carried the same reaction he had obtained as main product the alcohol $\text{R}(\text{CH}_2)_2\text{OH}$. He accepted that ethylene oxide had displaced the diethyl ether in the etherate, that is, instead of obtaining the compound given by eq (4)



he had prepared

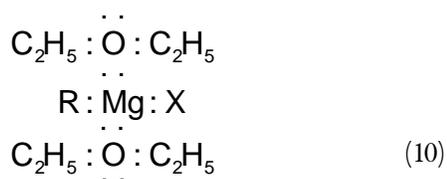


The second complex decomposed under the action of heat and in the presence of water, without necessarily following the fixation method but with valence permutation yielding first the bromomagnesium alcoholate, followed by hydrolysis to the alcohol



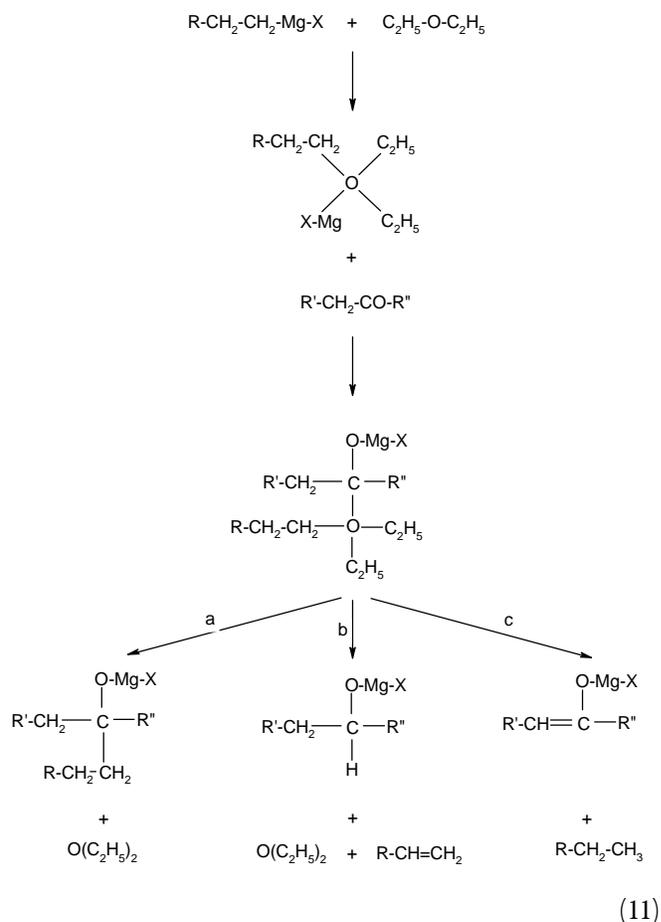
Thus, the difference between Grignard's and Blaise's results was due to the experimental conditions under which the reaction was conducted. According to Grignard, Blaise had not carried the reaction to completion and his ethylene bromhydrin originated from the reaction between ethylene oxide and magnesium bromide.

It is certainly possible that two molecules of ether enter in the formation of the etherate. At present the coordination formula

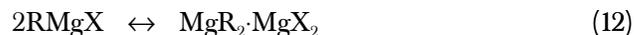


which can be readily carried over to the dietherates and compounds with tertiary amines, sulfide, etc., seems to fit the facts best. In structure (10) the magnesium atom completes its octet accepting electrons from the oxygen atom in the ether.

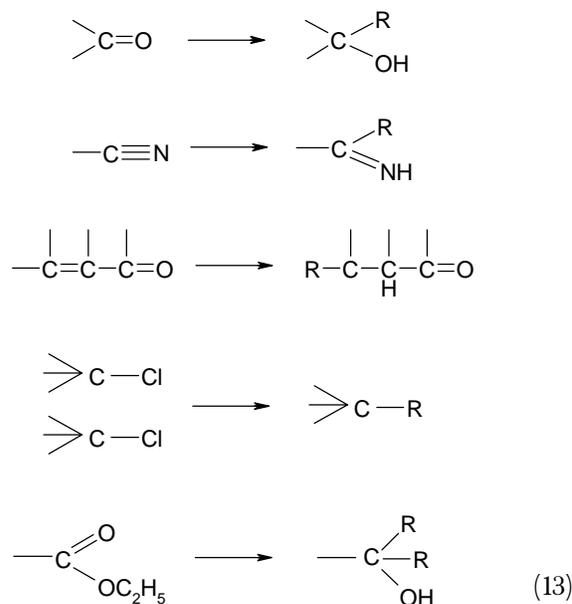
Grignard justified his formulate of the etherate on similar arguments as those expressed by structure (10): it maintains a direct link between the halogen atom and magnesium, and permits interpreting without difficulty the three reactions that take place between a organomagnesium compound and a ketone: (a) formation of a tertiary alcohol by a normal reaction, (b) formation of a secondary alcohol by hydrogenation and, (c) enolisation of the ketone. These three processes can be expressed as follows (Cologne, 1950):



Considering the data available for the different Grignard reactions, and the fact that in the presence of ether a equimolar mixture of MgR_2 and MgX_2 behaves in the same manner as a Grignard reagent prepared from RX and Mg , leads to the following conclusion: Grignard's organomagnesium compounds prepared in ether contains both the symmetric and mixed etherates; the two forms are in equilibrium whose position is regulated by the nature of R and X :



A summary of the findings about organomagnesium compounds indicates that similarly to all other organometallic compounds, they behave as reducing agents, allowing an organic compound that exists in a degree n of oxidation, to pass a degree $n-1$, $n-2$, or $n-3$. Organomagnesium compounds have the faculty of attaching R-H instead of H-H on organic molecules, by acting by addition over a opening double or triple bond; by opening a system of two multiple bonds, or by replacing a halogenated group or an alkoxy group by an alkyl radical. Symbolically (Cologne, 1950):



Grignard expressed the versatility of his compounds as follows: “Comme un violon bien réglé, les magnésiens peuvent, sous des doigts habiles, donner encore naissance aux accords les plus imprévus et les plus harmonieux” (The same like a well-tuned violin, organomagnesium compounds can, under the action of skilled fingers, give birth to the most unforeseen and harmonious accords) (Grignard, 1926).

Grignard’s research activities were not limited to organomagnesium halides. He made significant contributions to the chemistry of organoaluminum compounds, terpenes, acetylenic compounds, and condensations and reductions under reduced pressure. During World War I he contributed significantly to the study of the degradation action of aluminum chloride on alkylated benzenes with a view of increasing supplies of toluene for the manufacture of TNT. As director of one of the research laboratories on war gases he carried extensive investigations on the analysis and synthesis of mustard gas, phosgene, and other war gases.

The number of publications dealing with the new field of research grew at an amazing rate, by the end of 1905 they numbered 200, in 1912 they were over 700, by the end of

Grignard’s life (1935) they exceeded 6000. Today, the Scifinder database (Chemical Abstract) carries near 30,000 entries under the title Grignard reaction. ■

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