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Grignard reagents are a class of organic compounds consisting of alkyl- or aryl-magnesium halogens (e.g. methyl-, ethyl-, butyl-, phenyl-, bromo- and iodide-magnesium reagents) and metal salts (usually halogens) of other elements (e.g. copper, zinc, iron, etc.). Grignard reagents are named after Franz Grignard, the German chemist who first described this type of organic compound in 1900.Grignard reagents are widely used in organic chemistry, especially in the synthesis of complex organic molecules. They can be used to add alkyl or aryl groups to ketones, aldehydes, carboxylic acids, ether and other compounds. These reactions can be very useful as they allow the synthesis of complex organic molecules from simpler precursors. Grignard reagents are also used as catalysts, in the synthesis of some polymers and in other industrial research. However, Grignard reagents are extremely reactive and pyrophoric, i.e. they can ignite on contact with air or water, therefore require special conditions for storage and use, as well as safety precautions when handling them. Organic Chemistry: Synthesis of a Grignard Reagent Video: Organic Chemistry: Synthesis of a Grignard Reagent The history of the development of Grignard reagents began with the work of Franz Grignard, a German chemist, who first described this type of organic compound in 1900. In his work, Grignard described a method for producing magnesium halogens (chlorides, bromides and iodides) and using them for synthesizing new organic compounds such as alkenes, alkanes, ketones and aldehydes. This method became known as the “Grignard reaction”. In the 1950s, Grignard reagents were widely used in the synthesis of organic compounds, leading to a significant development in organic chemistry. Today, Grignard reagents remain an important tool for the synthesis of complex organic molecules and continue to attract the attention of chemists around the world because of their potential applications in medicine, electronics and other industries. The basic principle behind the reactivity of Grignard reagents is their ability to act as strong nucleophiles due to the polarized carbon-magnesium bond. The carbon atom of the alkyl or aryl group in the Grignard reagent is negatively charged due to the electronegativity difference between carbon and magnesium. As a result, the carbon atom becomes highly reactive and can attack electrophiles, such as carbonyl compounds, to form new carbon-carbon bonds. Another important principle of Grignard reagents is their high sensitivity to moisture and air. The polarized carbon-magnesium bond is very reactive towards water and oxygen, which can lead to the decomposition of the Grignard reagent and the formation of undesirable byproducts.Grignard reagents also exhibit strong basicity due to the presence of the negatively charged carbon atom. This can lead to the deprotonation of acidic compounds, such as alcohols or carboxylic acids, to form alkoxides or carboxylates. The resulting alkoxides or carboxylates can then react with electrophiles to form new carbon-carbon bonds. Overall, the basic principles of Grignard reagents involve their strong nucleophilicity, sensitivity to moisture and air, and strong basicity. These properties make Grignard reagents valuable tools in organic synthesis for the formation of new carbon-carbon bonds and the synthesis of a wide variety of organic compounds. The Grignard reaction – making a C-C bond. Grignard reagents are magnesium halogens of the general formula RMgX, where R is an organic radical and X is a halogen (usually bromine or chlorine). The structure of Grignard reagents has a complex multi-dimensional structure. The magnesium ion ($Mg2+$) has an octahedral geometry, surrounded by six ether or THF molecules. The magnesium ions combine with each other through bromide or chloride ions to form dimers. Thus, each Grignard reagent contains two RMgX groups bonded through a magnesium ion. Each RMgX group consists of radical R bonded to magnesium through a covalent bond and halogen X bonded to magnesium through an ionic bond. The radical R can be any organic radical, such as an alkyl, an aromatic radical, or a functional group such as a carbonyl group. Molecular model of a complex of methyl-magnesium chloride, a Grignard reagent, in which two molecules of tetrahydrofuran, THF, are bound to magnesium. The model is based on the crystal structure. Grignard reagents react with a wide range of organic compounds to form new bonds. The mechanisms of reactions with Grignard reagents depend on the nature of the reagent and reagent, as well as the reaction conditions. One of the most common reaction mechanisms of Grignard reagents is nucleophilic substitution, where the Grignard reagent attacks the electrophilic functional group in the organic compound. For example, a Grignard reagent can react with a ketone to form an alcohol: Grignard reagents in nucleophilic substitution Another reaction mechanism with Grignard reagents is the addition to the double bond in an organic compound, forming a new single bond. For example, a Grignard reagent can react with an alkene to form an alcohol: Grignard reagents in the addition to the double bond Grignard reagents can also react with halogens to form halogens: Grignard reagents with halogens It is important to note that reactions with Grignard reagents are stereoselective, i.e. a certain isomer can form with a higher degree of preference. Grignard reagents are widely used for the synthesis of organic compounds. These compounds can have different functional groups, such as alkenes, amines, alcohols and carbonyl compounds.The process of synthesizing organic compounds using Grignard reagents consists of reacting a Grignard reagent (usually an alkyl or aryl-magnesium halogen) with an organic compound containing an electrophilic functional group, such as a carbonyl group. The reaction leads to the formation of a new bond between molecules and the formation of complex organic compounds. Synthesis of organic compounds using Grignard reagents can be used in many applications, including pharmaceuticals, plastics and polymers, catalysts and dyes, synthesis of new materials, etc. Reactions of the Grignard reagent with carbonyl compounds. In addition to the synthesis of organic compounds, Grignard reagents are also widely used as catalysts and precursors for semiconductor materials. The catalysts obtained with Grignard reagents can be used to activate various chemical reactions such as polymerization and oxidation. For example, nickel-based catalysts produced with Grignard reagents can be used in the manufacture of plastics and rubber products. Grignard reagents are also used in the production of semiconductor materials to produce optoelectronic devices such as lasers and photodiodes or materials used in the production of solar cells, microelectronic devices and transistors. Reactions of the Grignard reagent with other electrophiles. Generation of the Grignard Reagent: Assemble the 5mL conical vial, the Claisen head, and the Drierite-charged drying tube. Flask1: Fill up with dry diethyl ether. Flask 2: Fill Flask #2 with 76µl of bromobenzene (Approximate the volume assuming that 20 drops equals 1mL in order to minimize/avoid inhaling the vapors and adding water). Add 0.5mL of ether from flask 1. Cap and mix the contents. Flask 3: Using a pair of tweezers place 3 pieces of dried magnesium turnings (in excess) in flask 3. Add 100µl of the solution from flask 2, followed by a small grain of iodine (serving as a kind of catalyst, one chemical method to initiate sluggish Grignard reactions). At this point, the magnesium turnings should be covered by the added solution. If no, add enough ether to cover the magnesium, but not too much or it will be too dilute. With the dried stirring rod press gently on the magnesium turnings in order to break their surface and to expose the fresh, unoxidized magnesium metal to the reaction mixture. Immediately assemble the apparatus and start to heat it gently. Before adding the remaining bromobenzene solution, you should observe signs of reaction initiation in the flask 3. These signs include appearance of bubbles on the Mg surface, cloudiness and disappearance of the purple iodine color. NOTE: Since ether is a low-boiling solvent, it is important to keep the reaction mixture from running dry of ether. Keep a close eye on the level of the reaction mixture and replenish any lost ether by adding more fresh ether from flask 1 with needle. (Do not open the rubber cap). On the other hand, adding too much ether may drastically lower the concentrations of the reacting species and slow down or stop the reaction. After the reaction is initiated, quickly add the spin vane in order to have constant stirring and then add the remainder of the bromobenzene solution drop-wise while stirring and gently heating. After the addition of bromobenzene is complete, transfer 300 µL of dry diethyl ether into flask 2, mix and dissolve any leftover bromobenzene and add it to the reaction flask. Keep stirring for 5 more minutes.II. Addition of Benzophenone: Prepare a solution of 105 mg of benzophenone (you can use the same needle that you have been using, no need of rinsing) in 300µL of diethyl ether in flask 4. When the 5 minutes of stirring (from part 1) is completed, add the benzophenone solution to the reaction over a 30 second-period, drop- wise (reaction is very quick. You should add it slowly. Don’t get too hot). The rate of addition should be such that a gentle reflux is never exceeded (you should not see bubbling). Dissolve any remaining benzophenone with 300µL of dried ether and add it to the reaction flask to increase the yield. Keep stirring for 5-10 minutes. Detach the reaction flask and let cool. Add 1.5 ml aqueous HCl drop-wise and stir to neutralize the solution and make alcohol. (If you don’t have enough to see two layers, add more ether). Cap, shake and let settle. Separate the two layers. Extract any residual amount of the organic compounds from the aqueous layer by using two 0.5ml portions of ether. Do back extraction to collect triphenylmethanol which was very slightly soluble in water due to its –OH group. Combine all the organic layers and dispose of the aqueous layer. Dry the organic layer using sodium sulfate. Evaporate all of the solvent over a hot plate. At this point you are be left with a mixture of triphenylmethanol and biphenyl. In order to separate these: Pour 10ml of petroleum ether on the solid mixture. It will dissolve the biphenyl but not the triphenylmethanol. Decant the liquid & rinse the solids with another 2ml of petroleum ether. The overall reaction sequence of synthesis of Triphenylmethanol. Grignard reagents can be hazardous to humans and require special care when working with them. They can be toxic and easily flammable in air, so special precautions are necessary.When working with Grignard reagents, laboratory safety rules have to be performed, such as the use of laboratory gloves, protective glasses and robe, and working in a well-ventilated room. Contact of Grignard reagents with oxygen from the air must also be avoided, which may cause them to ignite.When storing Grignard reagents certain storage conditions must be observed, such as storage in closed containers, separate from other chemicals, at a certain temperature and under conditions that exclude the possibility of ignition. Grignard reagents can be hazardous to the environment. In conclusion, Grignard reagents are an important tool in modern organic chemistry and have a wide range of applications in various fields, including synthesis of organic compounds, catalysis and semiconductors as well as medicine. However, working with Grignard reagents requires special attention to safety and adherence to the rules of laboratory practice. These reagents are toxic, flammable, air- and moisture-sensitive, therefore storage, transport and disposal regulations must be observed.The use of Grignard reagents can greatly expand the possibilities for the synthesis of organic compounds, facilitate the preparation of many industrial and scientific products and accelerate the development of many branches of science and technology. The Grignard Reagents Dietmar Seyferth Organometallics 2009, 28, 6, 1598–1605 Publication Date: March 16, 2009 American Chemical Society URL: Mechanism of Grignard reagent formation. The surface nature of the reaction H. M. Walborsky Acc. Chem. Res. 1990, 23, 9, 286–293 Publication Date: September 1, 1990 URL: Handbook of Grignard Reagents Gary S. Silverman, Philip E. Rakita CRC Press, 25.04.1996 Pages: 736 URL: Grignard reagent formation John F. Garst, Manuel P. Soriaga, Coordination Chemistry Reviews Volume 248, Issues 7–8, April 2004, Pages 623-652 URL: The constitution of the Grignard reagent A. D. Vreugdenhil, C. Blomberg Recueil des Travaux Chimiques des Pays-Bas Volume 82, Issue 5 1963 Pages 453-460 URL: Application of Grignard Reagent: the Grignard reagent is a useful intermediate reagent in organic chemistry. The Grignard reaction is an organometallic chemical reaction in which alkyl, vinyl, or aryl-magnesium halides add to a carbonyl group in an aldehyde or ketone. By this reagent alkanes, alcohol, aldehydes, ketones, carboxylic acid could be prepared. A number of compounds produced by the Grignard reaction are very precious and unique intermediates or products in the field of pharmaceutical, fragrance, and other excellent or specialty chemicals.A number of compounds produced by the Grignard reaction are very precious and unique intermediates or products in the field of pharmaceutical, fragrance, and other excellent or specialty chemicals.These reagents were revealed by the French chemist Victor Grignard, who won the Nobel Prize in Chemistry in the year 1912 for his work on these compounds.(i) Synthesis of hydrocarbon: Being hydrolyzed by water Grignard reagent forms hydrocarbons.RMgX + H_2O → R – H + Mg (OH) XExample: $CH_3MgI + H_2O$ → CH_4 + Mg (OH) IR-MgBr is the Grignard reagent. It forms this carbanion, R- (like CH_3CH_2-) This carb-anion can behave in two different ways. Further, the carb-anion can act as a nucleophilic and add into carbonyl groups with acid chlorides, esters, etc.(ii) Synthesis of alcohol: Grignard reagent reacts with different carbonyl compounds forming an unstable transition stage of a compound which by hydrolysis forms different alcohols. The Grignard Reaction is the addition of an organo-magnesium halide (Grignard reagent) to a ketone or aldehyde, to form tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to primary alcohol.When methanal reacts with Grignard reagent, it forms primary alcohol. In the case of other aldehydes, secondary alcohols are formed. In the case of ketones, tertiary alcohols are formed.Grignard reagents usually are organized by a reaction of an organ halogen with magnesium in a nitrogen atmosphere because the reagent is very immediate toward oxygen and moisture. Organ halogens differ significantly in their rates of reaction with magnesium. For example, alkyl iodides usually react exceedingly fast, whereas most aryl chlorides react gradually, if at all.(iii) Grignard reagents and water:Grignard reagents react with water to produce alkanes. This is the cause that everything has to be very dry during the preparation above.For example:The inorganic product, Mg(OH)Br, is referred to as a “basic bromide”. You can think of it as a sort of half-way stage between magnesium bromide and magnesium hydroxide.(iv) Reaction with Acidic Hydrogens:This can also be used to convert alkyl halides to alkanes. First, you care for it with magnesium, and then you indulgence the Grignard with a strong acid. This gives you the alkane. The first stride is to make the Grignard reagent. The second is to indulgence that Grignard with a deuterated acid such as D_2O. This gives you the deuterated alkane.Finally, Grignard reagents are enormously constructive organ metallic compounds in the field of organic chemistry. They show strong nucleophilic qualities and also have the capability to form new carbon-carbon bonds. Reactions >> Name Reactions The Grignard Reaction is the addition of an organomagnesium halide (Grignard reagent) to a ketone or aldehyde, to form a tertiary or secondary alcohol, respectively. The reaction with formaldehyde leads to a primary alcohol. Grignard Reagents are also used in the following important reactions: The addition of an excess of a Grignard reagent to an ester or lactone gives a tertiary alcohol in which two alkyl groups are the same, and the addition of a Grignard reagent to a nitrile produces an unsymmetrical ketone via a metalloimine intermediate. (Some more reactions are depicted below) Mechanism of the Grignard Reaction While the reaction is generally thought to proceed through a nucleophilic addition mechanism, sterically hindered substrates may react according to an SET (single electron transfer) mechanism: With sterically hindered ketones the following side products are received: The Grignard reagent can act as base, with deprotonation yielding an enolate intermediate. After work up, the starting ketone is recovered. A reduction can also take place, in which a hydride is delivered from the β-carbon of the Grignard reagent to the carbonyl carbon via a cyclic six-membered transition state. Additional reactions of Grignard Reagents: With carboxylic acid chlorides: Esters are less reactive than the intermediate ketones, therefore the reaction is only suitable for synthesis of tertiary alcohols using an excess of Grignard Reagent: With nitriles: With CO_2 (by adding dry ice to the reaction mixture): With oxiranes: Recent Literature Mechanochemical synthesis of magnesium-based carbon nucleophiles in air and their use in organic synthesis R. Takahashi, A. Hu, P. Gao, Y. Gao, Y. Pang, T. Seo, J. Jiang, S. Maeda, H. Takaya, K. Kubota, H. Ito, Nat. Commun., 2021, 12, 6691-6701. Added-Metal-Free Catalytic Nucleophilic Addition of Grignard Reagents to Ketones H. Zong, H. Huang, J. Liu, G. Bian, L. Song, J. Org. Chem., 2012, 77, 4645-4652. Zinc(II)-Catalyzed Addition of Grignard Reagents to Ketones M. Hatano, O. Ito, S. Suzuki, K. Ishihara, J. Org. Chem., 2010, 75, 5008-5016. 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Szymoniak, Synthesis, 2002, 1115-1120. A General Method to Access Sterically Encumbered Geminal Bis(boronates) via Formal Umpolung Transformation of Terminal Diboron Compounds P.-F. Ning, Y. Wei, X.-Y. Chen, Y.-F. Yang, F.-C. Gao, K. Hong, Angew. Chem. Int. Ed., 2023, 62, e202315232. Synthesis of 2-Substituted Pyridines via a Regiospecific Alkylation, Alkynylation, and Arylation of Pyridine N-Oxides H. Andersson, F. Almqvist, R. Olsson, Org. Lett., 2007, 9, 1335-1337. Organometallic coupling reaction Classical Grignard reaction Named after Victor Grignard Reaction type Coupling reaction Reaction Methanal/Higher aldehyde/Ketone + R-MgX + (H_3O+) ↓ Primary/Secondary/Tertiary alcohols Identifiers Organic Chemistry Portal grignard-reaction RSC ontology ID RXNO:0000014 A solution of a carbonyl compound is added to a Grignard reagent. (See gallery) An example of a Grignard reaction (R2 or R3 could be hydrogen) The Grignard reaction (French: [ɡʁiɲaʁ]) is an organometallic chemical reaction in which, according to the classical definition, carbon alkyl, allyl, vinyl, or aryl magnesium halides (Grignard reagent) are added to the carbonyl groups of either an aldehyde or ketone under anhydrous conditions.[1][2][3] This reaction is important for the formation of carbon–carbon bonds.[4][5] Grignard reactions and reagents were discovered by and are named after the French chemist François Auguste Victor Grignard (University of Nancy, France), who described them in 1900.[6] He was awarded the 1912 Nobel Prize in Chemistry for this work.[7] The reaction of an organic halide with magnesium is not a Grignard reaction, but provides a Grignard reagent.[8] Although Grignard reagents undergo many reactions, the classical Grignard reaction refers only to the reaction of RMgX with ketones and aldehydes, shown in red. X = Cl, Br, I. Classically, the Grignard reaction refers to the reaction between a ketone or aldehyde group with a Grignard reagent to form a primary or tertiary alcohol.[1] However, some chemists understand the definition to mean all reactions of any electrophiles with Grignard reagents.[9] Therefore, there is some dispute about the modern definition of the Grignard reaction. In the Merck Index, published online by the Royal Society of Chemistry, the classical definition is acknowledged, followed by "A more modern interpretation extends the scope of the reaction to include the addition of Grignard reagents to a wide variety of electrophilic substrates."[9] This variety of definitions illustrates that there is some dispute within the chemistry community about the definition of a Grignard reaction. Shown below are some reactions involving Grignard reagents, but they themselves are not classically understood as Grignard reactions. Additional reactions which involve Grignard reagents, but are not considered to be Grignard reactions by the classical definition. X = Cl, Br, I. See also: Grignard reagents § Reactions of Grignard reagents Because carbon is more electronegative than magnesium, the carbon attached to magnesium acts as a nucleophile and attacks the electrophilic carbon atom in the polar bond of a carbonyl group. The addition of the Grignard reagent to the carbonyl group typically proceeds through a six-membered ring transition state, as shown below.[10] The mechanism of the Grignard reaction.Based on the detection of radical coupling side products, an alternative single electron transfer (SET) mechanism that involves the initial formation of a ketyl radical intermediate has also been proposed.[11] A recent computational study suggests that the operative mechanism (polar vs. radical) is substrate-dependent, with the reduction potential of the carbonyl compound serving as a key parameter.[12] If a Grignard reaction is performed in the presence of water, or any labile proton, the labile proton will quench the Grignard reagent as shown in the figure above.[3] The Grignard reaction is conducted under anhydrous conditions.[3] Otherwise, the reaction will fail because the Grignard reagent will act as a base rather than a nucleophile and pick up a labile proton rather than attacking the electrophilic site. This will result in no formation of the desired product as the R-group of the Grignard reagent will become protonated while the MgX portion will stabilize the deprotonated species. To prevent this, Grignard reactions are completed in an inert atmosphere to remove all water from the reaction flask and ensure that the desired product is formed.[13] Additionally, if there are acidic protons in the starting material, as shown in the figure on the right, one can overcome this by protecting the acidic site of the reactant by turning it into an ether or a silyl ether to eliminate the labile proton from the solution prior to the Grignard reaction. Other variations of the Grignard reagent have been discovered to improve the chemoselectivity of the Grignard reaction, which include but are not limited to: Turbo-Grignards, organocerium reagents, and organocuprate (Gilman) reagents. Turbo-Grignards are Grignard reagents modified with lithium chloride. Compared to conventional Grignard reagents, Turbo-Grignards are more chemoselective; esters, amides, and nitriles do not react with the Turbo-Grignard reagent.[14] An example reaction of forming a Turbo-Grignard with an ester group. A conjugated 1,4 addition using a Gilman reagent with an arbitrary R group The behavior of Grignard reagents can be usefully modified in the present of other metals. Copper(I) salts give organocuprates that preferentially effect 1,4 addition.[15] Cerium trichloride allows selective 1,2-additions to the same substrates. Nickel and palladium halides catalyze cross coupling reactions. Wikimedia Commons has media related to Grignard reactions. Grignard reagent Wittig reaction Horner–Wadsworth–Emmons reaction Barbier reaction Bodroux–Chichibabin aldehyde synthesis Fujimoto–Belleau reaction Organolithium reagents Sakurai reaction Indium-mediated allylation Alkynylation ^ a b Smith, Michael B.; March, Jerry (2007), Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (6th ed.), New York: Wiley-Interscience, ISBN 978-0-471-72091-1 ^ Chapter 19: Carboxylic Acids. Organic Chemistry 4e Carey. mhhe.com ^ a b c Ouellette, Robert J.; Rawn, J. David (January 1, 2014), Ouellette, Robert J.; Rawn, J. David (eds.), "15 - Alcohols: Reactions and Synthesis", Organic Chemistry, Boston: Elsevier, pp. 491–534, doi:10.1016/b978-0-12-800780-8.00015-2, ISBN 978-0-12-800780-8, retrieved November 6, 2023 ^ Shirley, D. A. (1954). "The Synthesis of Ketones from Acid Halides and Organometallic Compounds of Magnesium, Zinc, and Cadmium". Org. React. 8: 28–58. ^ Huryn, D. M. (1991). 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"Comprehensive Study of the Enhanced Reactivity of Turbo-Grignard Reagents*". Angewandte Chemie International Edition. 62 (25): e202302489. doi:10.1002/anie.202302489. PMID 36971042. S2CID 257765567. ^ Woodward, Simon (January 1, 2000). "Decoding the 'black box' reactivity that is organocuprate conjugate addition chemistry". Chemical Society Reviews. 29 (6): 393–401. doi:10.1039/B002690P. ISSN 1460-4744. Retrieved from " Grignard reaction reagents are considered an indispensable instrument in contemporary organic chemistry. Originally, François Auguste Victor Grignard, a French chemist, said that in 1900, these compounds revolutionized the ability of chemists to form new bonds. They’re remarkably flexible regarding the many-sided chemical action that can still be achieved with them. This is why they are still significant in contemporary laboratories. In the synthesis of molecules as well as in the formation of a carbon-carbon bond, it is ubiquitous that chemists will prefer Grignard reagents. In this blog, Grignard reagents are explained along with the role they play as a very important tool in chemistry. We will also consider the uses and risks associated with their use. Grignard reagents are organomagnesium halides alt, though they are employed mainly in complement with organic synthesis. Their overall structure is RMgX, where ‘R’ is assigned to a wide range of alkyls or aryls and ‘X’ for a halogen. These reagents are prepared by the reaction of an alkyl or aryl halide with magnesium in a dry solvent. In this case, the latter can be diethyl ether or tetrahydrofuran. a) Nucleophilic: These reagents are nucleophilic, which means that they donate an electron pair for the formation of a bond. b) Reactive Nature: Grignard reagents are very active species. This makes them very effective in the different chemical transformations. c) Moisture Sensitivity: They are also soluble in water and tend to disintegrate in aqueous conditions. Thus, they should not be handled in humid environments. That is why Grignard reagents are of great use in several reactions. They can form new carbon-carbon bonds, which is essential in synthesizing more complex organic molecules. In chemistry, the major use of Grignard reagents is that they are used as nucleophiles with an added reaction. This means they go for electrophilic carbons, usually in carbonyl compounds. Further, they abduct these carbons to other compounds to form different bonds. Here’s a breakdown of how these reagents typically work: Formation of the Grignard Reagent: First, it is customary to react with magnesium with an alkyl or aryl halide in anhydrous solvent to produce RMgX. a) Nucleophilic Attack: The organomagnesium reagent RMgX then coats Fletcheran electrophile, frequently a carbonyl carbon, to form a new bond. b) Hydrolysis: Lastly, the product is washed with water or an acid to remove the magnesium by-product, thus yielding the organic compound of interest. This process makes it possible for chemists to make alcohols, acids, and other organic molecules with ease. Grignard reagents are used in many organic reactions and, therefore, are handy in any laboratory. Now, we will dive into some of the most common applications: One principal application of Grignard reagents is in the preparation of alcohols. This takes place through the interaction of the Grignard reagents with carbonyl compounds such as aldehydes, ketones, and esters. a) Aldehydes + Grignard reagent = Secondary alcohol b) Ketones + Grignard reagent = Tertiary alcohol This reaction provides chemists with an easy avenue to synthesize numerous classes of alcohol molecules. These compounds are required in numerous sectors, such as the pharmaceutical and beauty industries. Grignard reagents produce carboxylic acids, which are one of the main types of reactions. The reagent can be precipitated with carbon dioxide (CO_2). In this, it forms a carboxylate ion that is then converted to carboxylic acid upon acidification. This reaction is important in the fabrication of acids that are in high demand in industries such as plastics and detergents industries. Coupling reactions are also conducted using Grignard reagents, which refer to a process whereby two molecules combine to make a new molecule. These reactions are very important in the synthesis of organic compounds, particularly those used in the formulation of drugs. The presented Grignard reagents are also useful for making carbon-carbon bonds in the synthesis of more complex compounds from simpler ones. This is especially applicable in pharmaceutical chemistry, whereby the reaction rate of chemical substances determines the time taken for the formulations to work. Despite all its advantages, it is worth noting that working with Grignard reagents can be quite an issue at times. Because of their high reactivity, they are capable of reacting with undesired compounds and producing undesired products. Below are some common issues chemists face and how they solve them: Grignard reagents are known to react violently with water, causing them to decompose. To counter this, chemists employ completely dry solvents and all the equipment they require in the process. It is also recommended that the reaction vessel be filled with the compound under an inert gas such as nitrogen or argon. This ensures that the environment is also free of moisture. Because Grignard reagents are so highly reactive, they can react with other functional groups in the molecule that are not desired. Chemists shield these delicate groups through the help of what is known as a protecting group. Later on, they are altered after the elaboration of the particular chemical reaction. Through these lessons on what chemists may face and doing what one can to avert them. Chemists can guarantee that their reactions with Grignard reagents will happen just as they desire them to. Grignard reagents are very effective methods, but since they are very reactive, they ought to be handled carefully. The following are the ways to handle precautions: a) Proper Storage: They maintain Grignard reagents in sealed containers, such as nitrogen, in an inert atmosphere. b) Protective Gear: Wear proper protective tools such as gloves and eye shield to minimize exposure to these solvents. c) Dry Atmosphere: It is beneficial to see the reagent in a dry environment because if moisture is present, it will react with the reagent. Paying attention to some measures will also minimize the likelihood of danger. This comes with the application of such reactive compounds in the lab. Grignard reagents are not only limited to academic laboratories but also have extensive uses in many industries. A distinctive use is in drug synthesis, where they are used in pharmaceutical manufacturing companies. Its uses are also evident in fragrance and in the preparation of food additives. This confirms the versatility of the products in different industries. Reagents of the Grignard reaction have become one of the key milestones and discoveries of organic chemistry. This allows for the creation of new carbon-carbon bonds. Owing to their high reactivity and handleability, they are unmatched analytical work tools in the modern laboratory and serve various operational needs. All of these reagents allow chemists to assemble molecules with fine tolerance of step-building reactions whether used in synthesizing alcohols, ketones, or carboxylic acids. Despite the imperfections and failures they may bring, chemists can make the best out of their benefits in handling and safety measures that are put in place. It is for this reason that Grignard reagents remain a useful tool in formulating synthesis in laboratories as well as in large-scale industrial establishments. Share — copy and redistribute the material in any medium or format for any purpose, even commercially. Adapt — remix, transform, and build upon the material for any purpose, even commercially. The licensor cannot revoke these freedoms as long as you follow the license terms. Attribution — You must give appropriate credit , provide a link to the license, and indicate if changes were made . You may do so in any reasonable manner, but not in any way that suggests the licensor endorses you or your use. ShareAlike — If you remix, transform, or build upon the material, you must distribute your contributions under the same license as the original. No additional restrictions — You may not apply legal terms or technological measures that legally restrict others from doing anything the license permits. You do not have to comply with the license for elements of the material in the public domain or where your use is permitted by an applicable exception or limitation . No warranties are given. The license may not give you all of the permissions necessary for your intended use. For example, other rights such as publicity, privacy, or moral rights may limit how you use the material. 1. Grignard Reagent Formation Flame-dry a round bottom flask equipped with a magnetic stir bar. Add magnesium (Mg, 1.1 equiv.) to the round bottom flask. Add a small amount of iodine (I_2, a few crystals). Addition of iodine is to help remove any MgO on the surface of the Mg. Removing MgO allows for Mg and the aryl/alkyl halide to come in contact and react. Sonication or addition of methyl iodide or 1,2-dibromoethane can also help with initiation. Cool the reaction mixture to 0 °C with an ice-water bath Slowly add a THF (1 M) solution of allyl bromide (1 equiv.) to the round bottom flask with magnesium. After adding the solution of allyl bromide, stir the reaction mixture for 3 h at room temperature. 2. Nucleophilic Addition In a separate flame-dried round bottom flask, add trans-cinnamaldehyde (0.85 equiv.) and THF (0.5 M with respect to trans-cinnamaldehyde) and cool to 0 °C. Slowly add the THF solution of the Grignard reagent (allyl-magnesium bromide) to the trans-cinnamaldehyde solution. After the addition, warm the reaction mixture to room temperature by removing the ice-water bath and stir for 4 h. Monitor the reaction progress via TLC by looking for the disappearance of trans-cinnamaldehyde. After reaction completion, cool the mixture to 0 °C with an ice-water bath. Slowly quench the reaction with a saturated aqueous solution of ammonium chloride (NH_4Cl). Transfer the mixture into a separatory funnel and extract the aqueous layer with ethyl acetate 3x. Combine the organic layers and wash with water and brine (a saturated aqueous solution of NaCl). Dry the organic layer with anhydrous $MgSO_4$, filter, and evaporate the solvent via rotatory evaporation. Purify the crude residue via flash column chromatography. The Grignard reaction is a useful tool for the formation of carbon-carbon bonds in organic synthesis. This reaction was discovered more than a century ago by a French Chemist named Victor Grignard for which he was rewarded a Nobel Prize in 1912. The Grignard reaction consists of two steps. The first step is reacting an organohalide with magnesium metal, usually present in the form of turnings. This leads to in situ formation of an organomagnesium halide A.K.A. Grignard reagent. The second step is the reaction between this reagent and a carbonyl-containing compound like aldehyde, ketone, or ester, and depending on the compound used, a secondary or tertiary alcohol, composed of organic portions from both the reagent and the carbonyl-containing compound, is produced. In this video, we will show a step-by-step protocol for preparing allylmagnesium bromide, a frequently used Grignard reagent in chemistry labs. This will be followed by the procedure for reacting this reagent with trans-cinnamaldehyde to obtain a secondary alcohol. Lastly, we will look at a couple of applications of this reaction. Prior to addition of the reagents, flame-dry a 50-mL flask and stir bar to remove all traces of water, then cool to room temperature under an atmosphere of nitrogen. This is critical as Grignard reagents are very sensitive to moisture. Next, add oven-dried magnesium turnings and a few crystals of iodine which will facilitate initiation of the reaction by removing any magnesium oxide coating from the metal. Subsequently, add 24 mL of anhydrous THF. Place the flask in an ice-water bath to mitigate the heat produced, and with stirring, slowly add allyl bromide via syringe. Then remove the flask from the ice-water bath and allow the reaction mixture to reach room temperature. To ensure completion of the reaction, use gas chromatography to monitor the consumption of allyl bromide. Once the Grignard reaction is ready for use, prepare for the next step in the reaction. Add to a flame-dried 200-mL flask and stir bar trans-cinnamaldehyde and 30 mL of anhydrous THF, and stir under a nitrogen atmosphere. This is important as in the presence of moisture the Grignard reagent will be destroyed, and will not react with the carbonyl-containing compound. Stir the trans-cinnamaldehyde solution at 0 degrees, and insert a double-tipped needle into the headspace, with the other end inserted into the headspace of the flask containing the Grignard reagent. Remove the nitrogen-filled balloon from the cinnamaldehyde, and add a nitrogen line to the Grignard flask. Apply positive pressure with the nitrogen line to transfer the Grignard reagent into the cinnamaldehyde. After the addition is complete, replace the double-tipped needle with a balloon attachment, remove the cold bath, and stir at room temperature. To determine whether the reaction is complete, use thin layer chromatography to monitor the consumption of trans-cinnamaldehyde. Once it has been determined that the reaction is complete, cool the mixture to 0 degrees, and, while stirring, carefully add 30 mL of saturated aqueous ammonium chloride solution and 50 mL of ethyl acetate. Separate the layers using a separatory funnel, and extract the aqueous layer with three 50-mL portions of ethyl acetate. Combine the organic extracts in the separatory funnel, and wash with 50-mL saturated aqueous sodium chloride solution. Remove traces of water from the combined organic layers by adding approximately 500 mg of magnesium sulfate, then filter off the solid and rinse with additional ethyl acetate. Concentrate the mixture under reduced pressure, and purify the crude material using flash column chromatography. To verify the structure of the product, dissolve 2 mg of the dried material in 0.5 mL deuterated solvent and analyze by proton NMR. Now that we have seen an example laboratory procedure, let’s see some useful applications of the Grignard reaction. Phorboxazole A is a natural product that is shown to exhibit potent antibacterial, antifungal, and antiproliferative properties, prompting efforts in developing synthetic procedures for its manufacture. The Grignard reaction is used in a key step of this synthesis, in which an oxazolyl-methylmagnesium bromide attacks a lactone carbonyl to form a hemiketal intermediate. While the Grignard Reaction is widely applied, side reactions can occur depending on the nature of substrate, and should be taken into account when designing a new synthesis. For example, if the substrate is a hindered carbonyl, the Grignard reagent can react as a base, deprotonating the substrate, and yielding an enolate. Upon work up, the starting material is recovered. Alternatively, a beta-hydride elimination reaction can take place, leading to the reduction of the carbonyl to alcohol. To suppress these side reactions, lanthanide salts such as cerium(III) chloride are added to the reaction, where the salts coordinate with the carbonyl oxygen, enhancing the carbonyl electrophilicity. This in turn enables the Grignard reagent to add to the carbonyl to give the desired product and decreases the rate of unwanted products. For instance, in the reaction between cyclopentylmagnesium chloride and cyclohexenone, the beta-hydride elimination product dominates, if no cerium three chloride is added. However, when the same reaction is performed in the presence of the cerium salt, the desired addition product is obtained in high yield.You’ve just watched JoVE’s introduction to the Grignard reaction. You should now understand the principles of the Grignard reaction, how to perform an experiment, and some of its applications. Thanks for watching! Grignard reaction describes the addition of alkyl magnesium halides to the carbonyl group of aldehyde or ketone. Grignard reaction This reaction is one of the most significant process for the formation of carbon-carbon bonds. In this reaction process alkyl, vinyl, or aryl magnesium halides are regarded as Grignard reagents. The Grignard reactions and reagents are named after the French scientist Francois Auguste Victor Grignard, who made the discovery and was honored with the 1912 Nobel Prize in Chemistry. Grignard reagent An alkyl bromide and magnesium metal react to create an organomagnesium reagent in the first step of a Grignard synthesis. The resulting “Grignard reagent” serves as a potent base as well as a powerful nucleophile. As a result of its nucleophilic nature, it can interact with the electrophilic carbon in a carbonyl group to form the carbon-carbon bond. Because of its basic nature, it will react with acidic substances such as alcohols, water, phenols, carboxylic acids, and thiols. As a result, the reaction environment must be absolutely anhydrous and free of acids. Grignard reagents can also create hydroperoxides when they interact with oxygen. So they are quite unstable when exposed to the air. Firstly, nucleophilic attack alkyl or aryl group of Grignard reagent on the carbonyl group of carbonyl compounds to give intermediate complex. Which on hydrolysis produces corresponding alcohols. Reaction mechanism of Grignard reaction The Grignard reagent reacts with water, alcohol acid, and amine to give corresponding hydrocarbons. E.g., Propylmagnesiumbromide produces propane gas when treated with water. $CH_3 – CH_2 – CH_2$ Mg Br + H_2O → $CH_3 – CH_2 – CH_3$ + Mg (OH) Br When the Grignard reagent is treated with an alkyl halide, a coupling reaction occurs to give alkane. This reaction is catalyzed by the cuprous ions. E.g., Methyl magnesium bromide reacts with methyl bromide to produce ethane. CH_3 – MgBr + CH_3Br → $CH_3 – CH_3$ + $MgBr_2$ a. The Grignard reagent reacts with carbon dioxide to give carboxylic acid. For example., methylmagnesium bromide reacts with carbon dioxide to give acetic acid. b. Reaction of the Grignard reagent with Sulfur dioxide SO_2 to produce alkane sulphinic acid. For example, reaction of methylmagnesium chloride with sulfur dioxide, SO_2 produces methanesulphinic acid. c. The Grignard reagent reacts with sulfur trioxide (SO_3), to give alkane sulphonic acid. E.g., Methanesulphonic acid is formed when methylmagnesium chloride reacts with sulfur trioxide (SO_3). Nitriles, in reaction with the Grignard reagent, produce Ketone. However, addition of the Grignard reagent with hydrogen cyanide produces the aldehyde. E.g., Acetonitrile, for example, produces acetone when reacted with methyl magnesium iodide. CH_3 – MgI + CH_3 – CN → $(CH_3)_2$ C = N -MgI + H_2O → CH_3 – CO – CH_3 + Mg (OH) I + NH_3 CH_3 – MgI + H – CN → CH_3CH = N -MgI + H_2O → CH_3 – CO – H + Mg (OH) I + NH_3 1. Reaction of Chloramine, and NH_2Cl with a Grignard reagent to produce amines. CH_3 – MgX + Cl – NH_2 → CH_3 – NH_2 + $MgXCl$ 2. Nitriles can be prepared by the reaction of Grignard reagents with cyanogen or cyanogen chloride. CH_3 – MgX + NCCl (cyanogen chloride) → CH_3 – CN + MgX(CN) 3. Grignard reagents can be used to prepare alkyl iodides. Iodine reacts with alkyl magnesium chlorides or bromides to produce the corresponding alkyl iodides. CH_3 – MgBr + I_2 → CH_3 – I+ MgICl The reaction environment must be absolutely anhydrous and free of acids. Morrison, R. T., & Boyd, R. N., Organic chemistry, Allyn and Bacon, Inc. 1987. March, J., Advanced Organic Chemistry, Wiley Eastern Limited, 1986. Skyes, P., A Guide Book to Mechanism in Organic Chemistry, Second edition, Orient Longman Ltd., 1988. About Author