

1.6: Addition of Organometallics - Grignard

Review of Reactivity

Last time we looked at a reaction in which a new carbon-carbon bond was made. Today, we'll look at another such reaction, one which is generally quite useful for synthesis, the assembly of larger carbon structures from smaller molecules.

First, let's look back over the reactions we've studied. We see some consistent patterns emerging in the addition reactions of carbonyl groups.

1. The carbonyl carbon is electrophilic. Nucleophiles add there.
2. If acid is present, the first step is attack of H^+ at the oxygen atom. The nucleophile adds to the carbonyl carbon, which is now quite electrophilic, in the second step of the reaction.
3. If acid is not present, the first step is the reaction of the nucleophile with the carbonyl carbon, a process in which the carbonyl oxygen becomes negatively charged. This step is followed by attachment of an H^+ to that oxygen.
4. Later steps, which depend upon the structure of the nucleophile, determine whether the overall reaction is addition or replacement of the oxygen by the nucleophilic atom.

Let's think a bit about the relationship between the presence of acid and the sequence of events. Remember that nucleophiles and Lewis bases react in the same way, by using an unshared electron pair to make a new bond. It isn't a surprise that molecules which are good (strong) Lewis bases are also good (strong) nucleophiles. Hydroxide ion (OH^-) is a strong base, as are most compounds which share the $-O^-$ functional group. It is also a strong nucleophile, which we see in its unassisted reaction with a carbonyl carbon in the base-catalyzed addition of water.

It is tempting to think that we could set up a really fast reaction if we used both acid to attack the carbonyl oxygen with H^+ , which would make the carbonyl carbon really electrophilic, and base to attack the carbon with the strong nucleophile OH^- . This sounds really attractive, but it doesn't work. What we've forgotten with this idea is that significant concentrations of acid and base can't exist in the same solution because they neutralize each other. We have to conclude that in acidic solutions, only weak bases like water can exist (the conjugate strong bases like those which include $-O^-$ functional group would be neutralized to give $-OH$ groups). Such weak bases are also weak nucleophiles and need the increased electrophilic character which comes when the carbonyl oxygen is attached to an H^+ . This is the pattern we saw when weak nucleophiles like water and alcohols reacted in acid-catalyzed addition of water and in acetal/hemiacetal formation.

Another way to look at this is to say that if a strong nucleophile is to be used we must stay away from acidic solutions. We've seen this pattern both in the base-catalyzed addition of water and in the formation of a cyanohydrin. Addition of acid would have destroyed the nucleophiles (converted OH^- to H_2O and CN^- to HCN) in these cases.

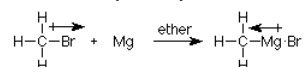
Grignard Reagent

We saw that the cyanide ion is a useful nucleophile and that its addition to a carbonyl group makes a carbon-carbon bond. Making carbon-carbon bonds is the central concern in organic synthesis, so it is important to find other compounds in which a carbon atom serves as a nucleophile. Let's think a bit about what that might mean.

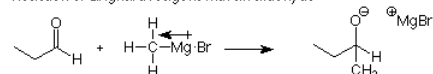
A nucleophile needs to have a pair of electrons to donate in order to make a new covalent bond. A carbon nucleophile would need to have an unshared pair or a bonding pair in which the polarity of the bond was such that the carbon was a strongly negative end of the dipole. That would imply that the carbon should be bonded to an atom which is less electronegative than carbon itself. A quick glance at the periodic table suggests that the bond will have to be between carbon and a metal. While there are many metals, we will look at only one, magnesium.

In the early part of the 20th century, Victor Grignard, a French organic chemist (the French pronunciation of his name can be approximated as "greenyard") studied the reactions of bromoalkanes with magnesium metal. When he carried out these reactions in solutions with ether, he found that the magnesium dissolved, heat was released and the solution turned dark gray. If he added a ketone or aldehyde to this mixture, heat was again evolved and a light gray precipitate was formed. When he finished the reaction by adding aqueous acid to the mixture, he found that he had made an alcohol in which the carbon to which the bromine atom had been attached had now become bonded to the carbonyl carbon. The process is outlined as follows:

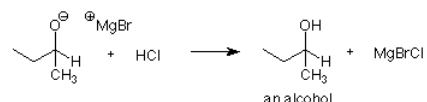
Formation of Grignard reagent



Reaction of Grignard reagent with an aldehyde



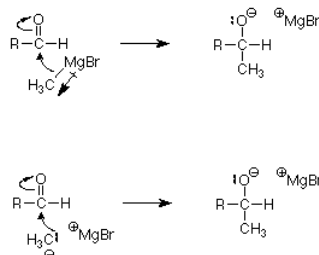
Reaction with acid



Since we have learned that the carbonyl carbon of aldehydes reacts as an electrophile, we must conclude that the carbon which started out attached to the bromine is behaving as a nucleophile. This can be understood if the magnesium is inserted between the bromine and the carbon, making a carbon magnesium bond which would be polarized so that the carbon is the negative end of the dipole. A compound with a carbon-magnesium bond is called a Grignard reagent. The details of the insertion of the magnesium atom into the carbon-bromine bond are not well understood, nor is the exact structure of the Grignard reagent itself. However, the reactivity of this reagent is symbolized effectively by the formula given.

Addition to Carbonyl Group

Let's look at the reaction of the Grignard reagent with the carbonyl carbon in a little more detail.

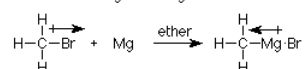


In the top reaction, the nucleophilic electron pair is shown as coming from the carbon-magnesium sigma bond, which is strongly polarized so that the electrons are much closer to the carbon. This makes the carbon nucleophilic. In the bottom reaction, the depiction of this bond is taken to an ionic extreme in which the electron pair is shown as entirely belonging to the carbon, which emphasizes the carbon's nucleophilic character. In this picture, the magnesium ion is "in the neighborhood" rather than being covalently bonded to the carbon. Such an extreme picture is probably an exaggeration, but it does emphasize the consideration of the attacking carbon as a nucleophile.

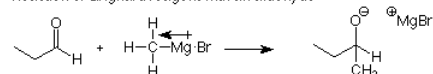
The picture of a carbon bearing an unshared electron pair also tells us that such a carbon would be a very strong base, much stronger than needed to take an H^+ from water to generate the weaker base OH^- . A practical consequence of this is that Grignard reagents must be kept dry, away from even the slightest traces of moisture, lest they be destroyed by reaction with water.

Now let's examine how we can use this overall reaction in synthesis. First, for economy in notation, let's develop a shorthand for the preparation of a Grignard reagent, its addition to a carbonyl group, and the reaction of that product with acid to make an alcohol. Here's the longhand version (repeated):

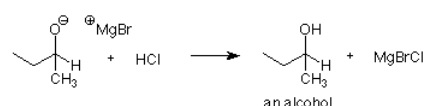
Formation of Grignard reagent



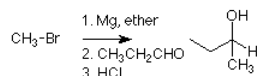
Reaction of Grignard reagent with an aldehyde



Reaction with acid



Now here's the shorthand version:



The shorthand version is interpreted to mean that

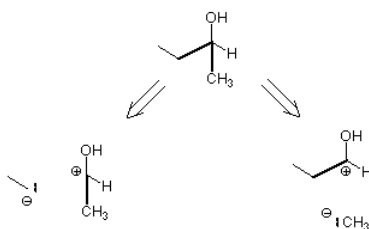
1. First we react bromomethane with magnesium metal using ether as a solvent. When this reaction is complete --
2. Second we add propanal ($\text{CH}_3\text{CH}_2\text{CHO}$) to this solution. After the second reaction is complete --
3. Third we add HCl to neutralize the O. and make the alcohol.

This represents a sequence of events carried out in the laboratory. In each numbered step all the reactants present are allowed to react before the next reaction is started. At the completion of each numbered step, the product could (in principle) be isolated and stored to be used later. In practice the high reactivity of water with Grignard reagents makes this very difficult, so it is not done.

This way of describing a sequence of laboratory events must not be confused with the sequence of steps which we used to describe a mechanism. When describing a mechanism we are tracing the path of single molecule at a time. At a given time, very few molecules are actually reacting; most are "resting" as either reactants which haven't gotten enough energy to proceed or products which have finished passing through the series of mechanistic steps. Usually, context will tell you which type of interpretation is meant. If you are in doubt, please ask.

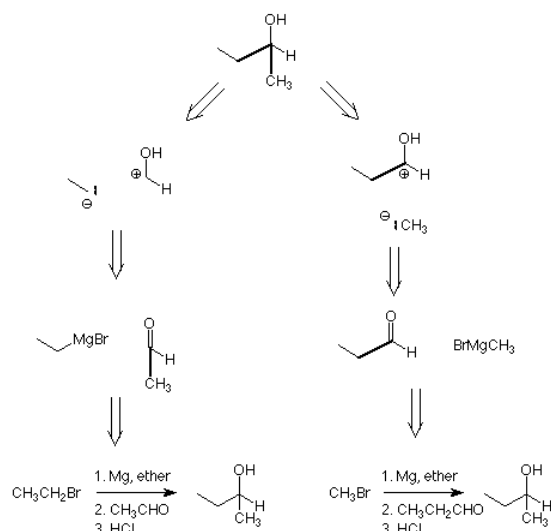
Thinking from Products to Reactants

Now, let's see how the addition of a Grignard reagent can be used in synthesis. If we look at the product of our shorthand description and remember that the addition of a Grignard reagent makes a new carbon-carbon bond in which one of the carbons is attached to an OH group, we can see that there are two such bonds (thicker and longer in the drawing) in our product molecule. Either is a candidate for being formed in the addition of the Grignard reagent. We can imagine the reagents needed for this to happen by simply erasing either of those bonds and examining what we get.



We remember that the bond came from an unshared electron pair on the Grignard reagent, and that the carbonyl carbon is electrophilic, so we show the appropriate charges. The structures we show here are not those of real molecules, but they serve to tell us which parts play what roles in the reactions. (The double-line arrows represent the direction of our thinking, not the direction of the actual reaction.)

In this way we arrive at a sketch of the reactants needed, which we need to turn into real reagents. We do this by remembering that the electrophilic carbon is provided by the carbonyl carbon and that the nucleophilic carbon comes from the Grignard reagent and then writing down what that tells us.



We finish up by placing the formation of the necessary Grignard reagent, its addition to the appropriate carbonyl compound, and the hydrolysis of the addition product in the appropriate sequence. This whole thought process is called "[retrosynthetic analysis](#)," but it is more simply regarded as *thinking backward from a goal to a process which will get you there*. It's a useful skill in organic chemistry and in many other areas.

If we do a few of these problems, we notice a pattern. If the carbonyl compound is formaldehyde, in the product there will be only one bond between the carbon attached to the OH group and another carbon (from the Grignard reagent). There will be two bonds between the OH-bearing carbon and hydrogens (from formaldehyde). Such an alcohol is called a primary alcohol, because the OH-bearing carbon is bonded to only one other carbon atom.

Similarly, if an aldehyde other than formaldehyde is used, the OH-bearing carbon in the product is bonded to two other carbons, and the alcohol formed is called secondary. Carrying this process one step further, the reaction of a ketone with a Grignard reagent gives a tertiary alcohol.

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