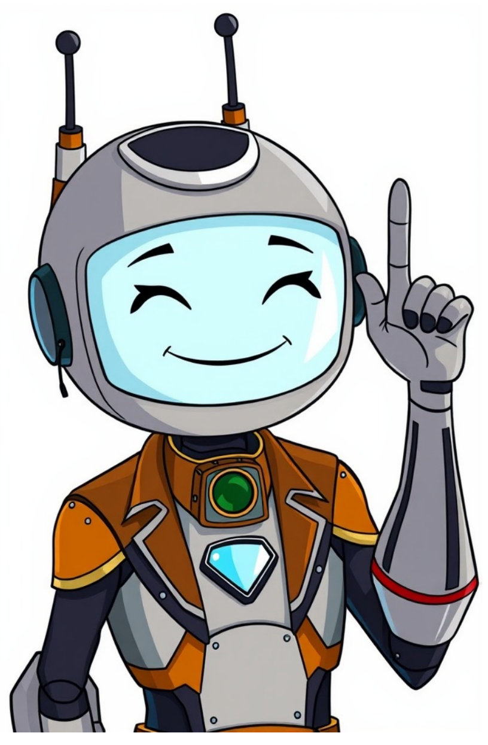

The provided text appears to be a collection of chemical reactions involving the reduction of a compound using LiAlH4, a strong reducing agent. The reactions involve varying conditions such as temperature, solvent choice, and reaction duration to optimize yields and selectivity. ================================== Purification of crude residue by silica gel chromatography and concentration in vacuo yields a colorless oil. [2.2 g, 47%] [Patent Reference: WO2015140133, page 104, (11.7 MB)] ================================== The reduction of carboxylic acids and esters is typically carried out using lithium aluminum hydride (LiAlH4). This reagent acts as a strong reducing agent, similar to sodium borohydride (NaBH4), but with a particular utility for carboxylic acid derivatives. ================================== LiAlH4 will reduce aldehydes and ketones to alcohols, as well as carboxylic acids and esters. However, it requires the addition of two hydrides to the carbonyl group in these compounds. Related reactions include the use of LiAlH4 with esters, which involves a nucleophilic acyl substitution followed by a nucleophilic addition. ================================== The reaction mechanism of LiAlH4 with an ester involves several steps. Firstly, the nucleophilic H from the hydride reagent adds to the electrophilic C in the polar carbonyl group of the ester. This creates an intermediate metal alkoxide complex. Secondly, the tetrahedral intermediate collapses and displaces the alcohol portion of the ester as a leaving group, producing a ketone as an intermediate. Finally, LiAlH4 reduces aldehydes by following a similar mechanism. ================================== Lithium aluminum hydride (LiAlH4) is a strong reducing agent that can reduce various functional groups in organic compounds. Its reactivity is comparable to sodium borohydride (NaBH4), but it offers advantages in certain reactions, particularly the reduction of esters to primary alcohols. However, its use may be limited by practical considerations and should only be employed when necessary. ================================== That NaBH4 will not is the reduction of carboxylic acids to primary alcohols. Other key reactions include acid halides to primary alcohols anhydrides to primary alcohols As well as reductions of nitriles, amides, epoxides, and alkyl halides (and more, which we won't cover) 3. Reduction of Carboxylic Acids By LiAlH4 – The Mechanism So how does the reaction of LiAlH4 with carboxylic acids work? Let's start with the basics. Carboxylic acids are acids. Lithium aluminum hydride is strongly basic. What might be the very first reaction to happen here? Click to Flip Yes – an acid-base reaction. Recall that the pKa of H2, the conjugate acid of hydride (H-) is about 36 whereas the pKa of the carboxylic acid is around 4. Since acid-base reactions are favored when a stronger acid will be converted to a weaker acid, this will rapidly generate the carboxylate salt (the conjugate base of the carboxylic acid) and hydrogen gas. (See article: How to Use a pKa Table). Acid-base reactions of LiAlH4 tend to be violently exothermic, and generate (flammable) hydrogen gas, besides. For these reasons extreme caution is used when handling LiAlH4 and it is never left out on the bench for any extended period, as it will react with water vapor from the air. Fires can result. [Note 3]. That's one key reason why NaBH4 is typically used for simple reductions – at cold temperatures, it reacts slowly and controllably with alcoholic solvents, unlike LiAlH4. In the presence of most nucleophiles, formation of a carboxylate signals the end of the reaction. We've seen that carboxylates will not undergo addition with most nucleophiles. (See article – Nucleophilic Acyl Substitution) LiAlH4 is an exception. [Note 4] In the first step, a hydride from aluminum forms a new C-H bond, breaking the C-O pi bond. In the second step, the C-O pi bond is re-formed, resulting in breakage of the C-O sigma bond. Nucleophilic acyl substitution on carboxylates is usually extremely difficult due to the strongly basic nature of the O(2-) leaving group, but the strong O-Al bond and aluminum's strongly Lewis acidic character likely greatly assists here. Elimination results in an aldehyde, which quickly undergoes another reduction. In theory, LiAlH4 has four equivalents of hydride that can be transferred, so it wouldn't be incorrect to draw AlH3 as the source of hydride here. In practice, an excess of LiAlH4 is generally used, and it's fine to draw this step of the mechanism as occurring from another equivalent of AlH4(-). This gives us the conjugate base of a primary alcohol (an alkoxide) coordinated to aluminum. To get our alcohol back, we perform a quench of the reaction with water, which protonates the alkoxide and gives us our neutral alcohol. That's how it works on paper, anyway! In practice, the workup is a little bit more complicated because aluminum salts make bitching emulsions that make isolation difficult unless they are completely hydrolyzed (yet another reason to just use NaBH4 if you can!) The Fieser workup is the industry standard, but there are others. [Note 3] ================================== LiAlH4 is a powerful reducing agent that eliminates even the weakest base to form new pi bonds. This usually occurs through the formation of C-O (pi) with loss of a leaving group, but in this case, it's not the C-O pi bond that forms - instead, it's broken and replaced by a C-N pi bond, resulting in an iminium intermediate and an alkoxide leaving group. The final product is an amine, which depends on the type of amide precursor used. Primary amides give primary amines, secondary amides give secondary amines, and tertiary amides give tertiary amines. LiAlH4 also reduces nitriles to primary amines, but this requires pretty forcing conditions. The reduction involves breaking a C-N (pi) bond and forming an imine species, followed by another addition of hydride to form a negatively charged nitrogen intermediate that's protonated to a primary amine during workup. Other reactions of LiAlH4 include reducing epoxides to alcohols, alkyl halides to alkanes in certain cases, and azides to primary amines. However, it won't reduce ethers. In summary, LiAlH4 is like the "T-rex" of reducing agents - powerful, readily available, and relatively cheap. But if you need a gentler touch, there are other options available, such as DIBAL or sodium borohydride (NaBH4), which are more selective but still effective. Note: LiAlH4 is more reactive than NaBH4 due to its Lewis-acidic lithium ion, but it's not suitable for all types of reductions. The workup process can be tricky with LiAlH4, requiring careful handling and precautions to avoid dust clouds, violent reactions with water and alcohols, and difficult emulsions with aluminum salts. One thing to keep in mind is that LiAlH4 has its limitations - it won't reduce certain functional groups, such as ethers. But for most types of reductions, especially those requiring forcing conditions or high temperatures, LiAlH4 is a reliable choice.The lab was in chaos when the LiAlH4 spontaneously combusted, destroying the analytical balance. Luckily, no one was injured. Meanwhile, a nap at his desk had suddenly ended for him due to the unexpected combustion of LiAlH4. ==================================___ Note 4. The Al-O bond is quite strong (128 kcal/mol), and since aluminum has an empty p-orbital for pi-bonding, the actual leaving group might be something akin to O=AlH2(-) which is considerably less basic than, say, O(2-)Li2 Note 5. The aldehyde can be formed under some conditions. For example using the strong reducing agent super-hydride (Lithium tri sec-butylborohydride) at low temperatures, the aldehyde can be obtained. A special class of amides known as Weinreb amides will undergo mono-addition by organometallic reagents (including hydride sources). These reactions work because the nitrogen contains a Lewis basic OCH3 group that can coordinate with the metal and help to stabilize the tetrahedral intermediate, preventing elimination. Note 6. Nitriles will undergo partial reduction with the use of DIBAL-H. They can also undergo addition by Grignard reagents to give ketones after hydrolysis of the resulting imine. Note 7. LiAlH4 is usually prepared through the reduction of a solution of AlCl3 in ether by lithium hydride (LiH). We generally don't think of the hydride ion in NaH and LiH as a good nucleophile, but given a strong enough Lewis base, it can act as one. Quiz Yourself! Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. Become a MOC member to see the clickable quiz with answers on the back. (Advanced) References and Further Reading For more context on reduction, this handout (PDF) on reducing agents from Prof. Andrew G. Myers' Chemistry 115 course at Harvard is an extremely useful overviewIn organic chemistry, aldehydes and ketones undergo reductions to form alcohols. Aldehydes produce 1º-alcohols, while ketones produce 2º-alohols. However, in metal hydrides reduction, the resulting alkoxide salts are insoluble and need hydrolysis before the alcohol product can be isolated. One useful reagent for this process is sodium borohydride (NaBH4). # NaBH4 works with a solvent system that achieves hydrolysis automatically. In the lithium aluminium hydride reduction, water is usually added in a second step. This leads to the formation of soluble inorganic salts at the end of either reaction. Note: LiAlH4 and NaBH4 can both reduce aldehydes and ketones to the corresponding alcohol. Mechanism for a LiAlH4 reduction: 1) Nucleophilic attack by the hydride anion 2) The alkoxide is protonated # Another useful reagent for this process is lithium aluminium hydride (LiAlH4). This reagent is prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Characteristics of LiAlH4: * It reacts violently with water, alcohols, and other acidic groups, evolving hydrogen gas. * It reduces carboxylic acids, esters, lactones, acid halides, and anhydrides to primary alcohols. * It also reduces nitriles and amides to amines and can open epoxides as well as reduce alkyl halides to alkanes. Improvement suggestions for the website (email) (No text provided) ================================== Strange that the negative charge appears on aluminum. Why is that? This might be a good opportunity to remind ourselves that formal charge isn't always the same as electron density. Hydrogen has an electronegativity of 2.2, while aluminum's is 1.61. So, even though aluminum bears a negative formal charge, it's actually the hydrogens with a partial negative charge and aluminum with a partial positive charge. Now, let's look at LiAlH4 reacting with water to see how it behaves as an acid donor. The reaction should involve a proper electron pushing arrow. Which one do you think will be more reactive - borohydride [BH4–] or AlH4(-)? Lithium borohydride (LiBH4) is actually more reactive than NaBH4 in some reactions. It's worth noting that the counter-ion can make a big difference. Now, comparing LiAlH4 and NaBH4 - both will reduce aldehydes and ketones, but for practical reasons, NaBH4 is preferred because it's easier to use. However, if you need to reduce other functional groups as well, using LiAlH4 might be necessary. One key difference between the two is that LiAlH4 can reduce esters more quickly than NaBH4 and also perform reductions on carboxylic acids, which NaBH4 cannot do. The mechanism of how LiAlH4 reacts with carboxylic acids involves an acid-base reaction. The strong basic nature of lithium aluminum hydride causes it to react violently with water vapor in the air, producing flammable hydrogen gas. Therefore, extreme caution is needed when handling LiAlH4. In this reaction, the C-O pi bond breaks first, followed by the formation of a new C-H bond. This results in the breakage of the C-O sigma bond. The process is similar to nucleophilic acyl substitution on carboxylates, but it's much easier due to the strong O-Al bond and aluminum's Lewis acidic character. The final product is an aldehyde, which then undergoes another reduction to form a primary alcohol. However, because lithium aluminum hydride has multiple equivalents of hydride, it can be used in excess to facilitate this reaction. ================================== LiAlH4 can be used to reduce esters to aldehydes, but that's not all - it also eats aldehydes for breakfast. Adding hydride to an ester forms a tetrahedral intermediate, followed by elimination of the alkoxide leaving group and formation of a C-N pi bond, resulting in an iminium intermediate. However, this doesn't last long and is quickly consumed by more hydrides. The final product obtained after workup is a primary alcohol. Unlike sodium borohydride, LiAlH4 can also reduce amides to amines, but the N-H bonds of primary and secondary amides must be weakly acidic for it to work. Primary amides give primary amines, secondary amides give secondary amines, and tertiary amides give tertiary amines. Another challenging functional group is the nitrile, which requires high forcing conditions to hydrolyze into carboxylic acids or amides. However, LiAlH4 can reduce nitriles to primary amines through an addition reaction that breaks a C-N pi bond and forms an imine species. The final product obtained after workup is a primary amine. LiAlH4 also has the ability to reduce epoxides to alcohols, which can be thought of as an SN2 reaction. In certain cases, it can reduce alkyl halides to alkanes, with preference for the least substituted carbon. Additionally, LiAlH4 can reduce azides to primary amines. However, there is one functional group that LiAlH4 will not touch: ethers.The Lewis-acidic nature of the lithium ion plays a crucial role in activating the carbonyl group towards nucleophilic attack, much like how protonated carbonyls are more reactive than neutral carbons. LiBH4 is less reactive compared to LiAlH4 but still capable of reducing esters to alcohols. Note 2 The reduction of carbonyl compounds is a crucial step in organic synthesis, allowing for the formation of alcohols from various functional groups. This process involves the addition of two hydrogen atoms to the C=O bond, resulting in the creation of an alkoxide ion. ================================== Using LiAlH4 as a reducing agent, the hydride ion reacts with the carbonyl group, facilitating the addition of hydrogen. The polar covalent nature of this bond enables the hydrogen to act as a hydride ion, which is highly reactive both as a base and a nucleophile. The presence of the π bond in the carbonyl group allows for the addition of H–, making LiAlH4 an efficient reducing agent. The high reactivity of LiAlH4 makes it incompatible with protic solvents, such as water. Therefore, reactions are carried out in dry solvents like anhydrous ether and THF. In contrast, NaBH4 is less reactive and can be used for selective reductions, such as the reduction of aldehydes and ketones in the presence of esters. The mechanism of LiAlH4 reduction involves two steps: the addition of the hydride ion to the carbonyl group, facilitated by the lithium ion acting as a Lewis acid. The resulting alkoxide salt can react with AlH3 to produce another source of hydride. However, for simplicity, we often show only one addition followed by protonation with water or an aqueous acidic solution to yield the final alcohol product. ==================================The electrophilicity of the carbon atom in an ester is partially suppressed by the lone pair of the oxygen through resonance stabilization, preventing NaBH4 from attacking it. In contrast, LiAlH4 can reduce esters to alcohols through a two-step process involving hydride additions and tetrahedral intermediates. ================================== ================================== The Power of LiAlH4: Reducing a Variety of Functional Groups ================================== LiAlH4 is a versatile reducing agent, often used in organic synthesis due to its ability to reduce a wide range of functional groups. At cold temperatures, NaBH4 reacts slowly and controllably with alcoholic solvents, whereas LiAlH4 exhibits different behavior. In the presence of most nucleophiles, carboxylate formation signals the end of the reaction. However, LiAlH4 is an exception. The reduction mechanism of LiAlH4 involves a series of steps. Initially, a hydride from aluminum forms a new C-H bond, breaking the C-O pi bond. This is followed by the re-formation of the C-O pi bond, resulting in the breakage of the C-O sigma bond. Nucleophilic acyl substitution on carboxylates is challenging due to the strongly basic nature of the O(2-) leaving group. The reduction mechanism of LiAlH4 with esters is simpler. Addition of hydride to the ester followed by elimination of alkoxide results in the formation of an aldehyde. However, LiAlH4 can reduce esters further to primary alcohols. The use of DIBAL (Di-isobutylaluminum hydride) or LiAlH(Ot-Bu)3 can help achieve this. Amides are another class of functional groups that are difficult to reduce. LiAlH4 reduces amides to amines, while NaBH4 does not react with them. The N-H bonds of primary and secondary amides undergo deprotonation by LiAlH4, resulting in the formation of their conjugate bases. The reduction mechanism of LiAlH4 with esters is even simpler. Addition of hydride to the ester followed by elimination of alkoxide results in the formation of an aldehyde. However, LiAlH4 can reduce esters further to primary alcohols. The use of DIBAL (Di-isobutylaluminum hydride) or LiAlH(Ot-Bu)3 can help achieve this. Finally, the reduction of nitriles to primary amines by LiAlH4 is also possible. Although it requires forcing conditions, LiAlH4 can hydrolyze nitriles into carboxylic acids or amides and then reduce them to primary amines.LiAlH4 is a powerful reducing agent that can tackle even the toughest functional groups, earning it the nickname "T-rex" among chemists. This hydride-adding beast can reduce nitriles to primary amines, break C-N (pi) bonds to form imine species, and even reduce epoxides to alcohols with remarkable efficiency. The first step in reducing nitriles involves breaking the C-N (pi) bond, which is followed by an addition of hydride to form a negatively charged nitrogen intermediate. This intermediate is then protonated to produce a primary amine during workup. Interestingly, it's possible to stop the reduction after one addition of hydride using DIBAL. LiAlH4 also has a knack for performing SN2 reactions with alkyl halides, converting them into chain-extended primary amines. Another fascinating property of LiAlH4 is its ability to reduce epoxides to alcohols, which shares some similarities with an SN2 reaction. In certain cases, it can even reduce alkyl halides to alkanes in the specified order. It's worth noting that there are some functional groups that LiAlH4 will not touch, such as ethers. For those situations where a gentler reducing agent is needed, derivatives like DIBAL and LiAlH(Ot-Bu)3 can be employed. Sodium borohydride (NaBH4) is also suitable for reducing aldehydes and ketones. In contrast to LiAlH4, which reacts violently with water and alcohols, sodium borohydride can be used in cold alcoholic solvents without incident. The workup of sodium borohydride reductions is relatively straightforward, whereas LiAlH4 requires more caution due to its reactivity and tendency to form dust clouds. Overall, LiAlH4 is an indispensable tool in any chemist's arsenal, offering a powerful and versatile reducing agent that can tackle even the most challenging functional groups.Reducing agents are crucial in many organic reactions, including the preparation of lithium aluminum hydride (LiAlH4), which is often synthesized through the reduction of a solution of AlCl3 in ether by lithium hydre (LiH). ================================== The LiH and AlCl3 combination forms a strong Lewis base, making it an effective nucleophile. When used as reducing agents, they can catalyze various organic reactions. ================================== However, there is evidence that suggests AlH and NaH are not typically viewed as effective nucleophiles in the right conditions but with enough of lewis bases they could act one. ==================================