Reactions with Organometallic Reagents

The facile addition of alkyl lithium reagents and Grignard reagents to aldehydes and ketones has been described. These reagents, which are prepared from alkyl and aryl halides, are powerful nucleophiles and very strong bases. Reaction of an excess of these reagents with acyl chlorides, anhydrides and esters leads to alcohol products, in the same fashion as the hydride reductions. As illustrated by the following equations (shaded box), this occurs by sequential addition-elimination-addition reactions, and finishes with hydrolysis of the resulting alkoxide salt. A common bonding pattern is found in all these carbonyl reactions. The organometallic reagent is a source of a nucleophilic alkyl or aryl group (colored purple), which bonds to the electrophilic carbon of the carbonyl group (colored orange). Substituent Y (colored green) is eliminated from the tetrahedral intermediate as its anion. The aldehyde or ketone product of this elimination then adds a second equivalent of the reagent.

Reactions of this kind are important synthetic transformations, because they permit simple starting compounds to be joined to form more complex structures. Esters are the most common carbonyl reactants, since they are cheaper and less hazardous to use than acyl chlorides and anhydrides. Most esters react with organometallic reagents to give 3°-alcohols; but formate esters (R=H) give 2°-alcohols. Some examples of these reactions are provided in the following diagram. As demonstrated by the last equation, lactones undergo ring opening and yield diol products.

The acidity of carboxylic acids and 1° & 2°-amides acts to convert Grignard and alkyl lithium reagents to hydrocarbons (see equations), so these functional groups should be avoided when these reagents are used.

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\begin{align*}
R\text{-CO}_2\text{H} + R'\text{MgBr} \quad &\quad \text{ether soln.} \quad R\text{-CO}_2\text{(-)}\text{MgBr(+) + R'-H} \\
R\text{-CONH}_2 + R'\text{Li} \quad &\quad \text{ether soln.} \quad R\text{-CONH(-)}\text{Li(+)} + R'-\text{H}
\end{align*}
\]
Since acyl chlorides are more reactive than esters, isolation of the ketone intermediate formed in their reactions with organometallic reagents becomes an attractive possibility. To achieve this selectivity we need to convert the highly reactive Grignard and lithium reagents to less nucleophilic species. Two such modifications that have proven effective are the Gilman reagent ($R_2CuLi$) and organocadmium reagents (prepared in the manner shown).

$$2 \text{R–MgBr} + \text{CdCl}_2 \xrightarrow{\text{ether & benzene}} \text{R}_2\text{Cd} + \text{MgBr}_2 + \text{MgCl}_2$$

Specific examples of ketone synthesis using these reagents are presented in the following diagram. The second equation demonstrates the low reactivity of organocadmium reagents, inasmuch as the ester function is unchanged. Another related approach to this transformation is illustrated by the third equation. Grignard reagents add to nitriles, forming a relatively stable imino derivative which can be hydrolyzed to a ketone. Imines themselves do not react with Grignard reagents.