Chapter 12 – Part 2

Reaction of Carbonyl Compounds with Organometallic Compounds

Organometallic Compounds = carbanions

- Carbon-metal bonds vary widely in character from mostly covalent to mostly ionic depending on the metal
- The greater the ionic character of the bond, the more reactive the compound
- Organopotassium compounds react explosively with water and burst into flame when exposed to air

Useful reagents - Organolithium and Organo-magnesium compounds

- Organolithium Compounds
  - Organolithium compounds can be prepared by reaction of an alkyl halide with lithium metal in an ether solvent
  - The order of reactivity of halides is R-I > R-Br > R-Cl (R-F is seldom used)

\[ R-X + 2 \text{Li} \rightarrow \text{RLi} + \text{LiX} \]
  
  (or Ar-\(X\))

Organo-magnesium Compounds = Grignard Reagents

- Grignard reagents are prepared by the reaction of organic halides with magnesium turnings
- An ether solvent is used because it forms a complex with the Grignard reagent which stabilizes it

\[
\begin{align*}
\text{RX} + \text{Mg} & \rightarrow \text{RMgX} \\
\text{ArX} + \text{Mg} & \rightarrow \text{ArMgX} \\
\text{CH}_3\text{CH}_2\text{Br} + \text{Mg} & \rightarrow \text{CH}_3\text{CH}_2\text{MgBr} \\
\text{C}_6\text{H}_5\text{Br} + \text{Mg} & \rightarrow \text{C}_6\text{H}_5\text{MgBr}
\end{align*}
\]

Reactions of Organolithium and Organo-magnesium Compounds

- With Compounds Containing Acidic Hydrogen Atoms
  - Organolithium and Grignard reagents behave as if they were carbanions and they are therefore very strong bases
  - They react readily with hydrogen atoms attached to oxygen, nitrogen or sulfur, or any compound with acidic hydrogens

\[
\begin{align*}
\text{R-MgX} + \text{H}_2\text{O} & \rightarrow \text{R-OH} + \text{Mg} + \text{X} \\
\text{R-MgX} + \text{H_2N} & \rightarrow \text{R-NH_2} + \text{Mg} + \text{X} \\
\text{R-MgX} + \text{H_2S} & \rightarrow \text{R-SH} + \text{Mg} + \text{X}
\end{align*}
\]
Organolithium and Grignard reagents can be used to form alkynes by acid-base reactions. Alkynylmagnesium halides and alkynyllithium reagents are useful nucleophiles for C-C bond synthesis.

Grignard reagents are very powerful nucleophiles. React with the δ+ carbons of oxiranes:
- Reaction results in ring opening and formation of an alcohol
- Reaction occurs at the less-substituted ring carbon of the oxirane
- Net result is carbon-carbon bond formation two carbons away from the alcohol

**Predict the product**

1. CH₃MgBr
2. H₂O

A. B. D. E. ?

**Reaction of Grignard Reagents with Carbonyl Compounds**

Reaction of Grignard reagents with aldehydes and ketones yields a new carbon-carbon bond and an alcohol.

**Mechanism**

1. Grignard reagent reacts with the ketone, forming an alcohol.
2. The alcohol is then further reacted with a second equivalent of Grignard reagent to form another alcohol.

**Alcohols from Grignard Reagents**

- Different classes of alcohols are formed depending on the starting carbonyl compound.

**Esters react with two molar equivalents of a Grignard reagent to yield a tertiary alcohol**

- The ketone is formed by first equivalent of Grignard reagent reacts immediately with a second equivalent to produce the alcohol.
- The final product contains two identical groups at the alcohol carbon that are both derived from the Grignard reagent.
Predict the product

1. CH₃MgBr
2. H₂O

A. B.
C. D.

Which carbonyl might be used to make 3-hexanol?

A. B. C. D.

Versatility of Grignard Syntheses

Example: Synthesis of 3-phenyl-3-pentanol
- The starting material may be a ketone or an ester
- There are two routes that start with ketones (one is shown)

Synthesize the following compound using an alcohol of 4 carbons as the only organic starting material
Grignard reagents are powerful bases as well as nucleophiles. Grignard reagents cannot be made from halides which contain acidic groups or electrophilic sites elsewhere in the molecule.

- Any acidic hydrogen atoms in the carbonyl substrate will react first, quenching the Grignard reagent.
- If Grignard is cheap, two equivalents of Grignard reagent could be used, so that after first equivalent is consumed, the second equivalent accomplishes carbon-carbon bond formation.

**Limitations on the Use of Grignard Reagents**

Overcoming limitations using protecting groups

- Silyl ether protecting group – from Ch. 11.11

Overcoming limitations using protecting groups

- Organolithium reagents react similarly to Grignard reagents.
  - Organolithium reagents tend to be more reactive.

- Sodium alkynides react with carbonyl compounds such as aldehydes and ketones to form new carbon-carbon bonds.

Other carbanions can also add to carbonyls

- Synthesize the following compound using reagents of 6 carbons or less.

- Synthesize this alcohol, using reagents of 6 carbons or less.
Synthesize this compound, using reagents of 6 carbons or less.


- This is an alternative formation of carbon-carbon bonds which, in effect, couples two alkyl halides.
- One of the halides is converted to a lithium dialkylcuprate by a two step sequence.
- Treatment of the lithium dialkylcuprate with the other halide results in coupling of the two organic groups.

These are the organic starting materials. The R− and R'− groups need not be different.