GRIGNARD ARYLAZTION OF 2-BUTANONE

CHM 234

Adapted from slides by Alisha Pitchford
The Grignard Reagent

- An organomagnesium halide (such as phenylmagnesium bromide) is commonly referred to as a Grignard reagent.
- Although the C–Mg bond is very polar, it is still covalent.
- Metal atoms are less electronegative than carbon. The polarity of a C–M bond is reversed in comparison to C–X, C–N, etc. found in a typical organic compound.
- The resulting δ− carbon creates a carbon nucleophile.

\[
\begin{array}{c}
\text{δ−} \\
R−\text{MgBr} \\
\text{δ+}
\end{array}
\]
The Grignard Reaction

- Although Grignard reagents are strongly nucleophilic, they only react well with carbonyl groups and epoxides.
- By forming new carbon-carbon bonds, Grignard reactions let us alter the backbone of a compound, rather than just its functional groups.
- The reaction of Grignard reagents is an important route to prepare alcohols.
- The type of carbonyl compound used determines the type of alcohol produced: aldehydes afford secondary alcohols, while ketones and esters yield tertiary alcohols. Primary alcohols can be prepared from the Grignard reaction of formaldehyde (CH₂O).

$$R-X \xrightarrow{1. \text{ Mg}} \xrightarrow{2. \text{ dilute acid}} OH \xrightarrow{3. \text{ dilute acid}} R$$
The Grignard Reaction

- The Grignard reagent is formed by reduction of the alkyl halide. (OK to consider this black magic until you take Professor Youmans’ course.)
- The reagent nucleophilically attacks the carbonyl.
- During workup, the alkoxide is protonated to give an alcohol.

\[ \text{R–X} \xrightarrow{\text{Mg, Et}_2\text{O}} \text{R–MgX} \]  

\[ \text{R–MgX} + \text{O} \rightarrow \text{R}^\text{O}^- \rightarrow \text{R}^\text{OH} \]
Preparing the Reagent

◦ Grignard reagents (R–MgX) are formed from the reaction of an alkyl halide and magnesium.
◦ The solvent is typically diethyl ether ("ether", Et₂O) or tetrahydrofuran (THF).
◦ The reaction occurs on the metal surface, and is sometimes difficult to start. Let your lab instructor know if you reaction has not started after 10 minutes.
◦ The reaction has started when the mixture becomes cloudy and generates enough heat to boil Et₂O without additional heat.

\[
\begin{align*}
\text{R–X} & \quad \xrightarrow{\text{Mg}} \quad \text{R–MgX} \\
\text{Et}_2\text{O} &
\end{align*}
\]
Anhydrous Reactions

- The Grignard Reagent is water sensitive: any traces of water will destroy it, preventing the desired reaction.

\[ \text{R–MgX} + \text{H}_2\text{O} \rightarrow \text{RH} + \text{HO–MgX} \xrightarrow{\text{RMgX}} 2 \text{RH} + \text{MgX}_2 + \text{MgO} \quad (3) \]

- It is crucial that the reaction apparatus, reagents, and solvents be kept dry. You will use oven-dried glassware for this experiment.

- We will similarly use drying tubes (which contain a desiccant) to absorb any moisture in the air that enters the glassware as it cools and during the reaction.

- The solvent is special anhydrous ether, which is stored in a sealed bottle.

- Make sure to keep the reagent bottles capped, to minimize absorption of atmospheric moisture.
The Grignard Reaction

- Grignard reagents react with carbonyl compounds to form alcohols. The type of alcohol produced depends on the type of carbonyl.

- In this experiment you will prepare a tertiary alcohol from a ketone. This process consists of two reactions:
  1. Formation of Grignard Reagent
  2. Reaction of Grignard Reagent to form the alcohol

\[
\begin{align*}
R-X & \xrightarrow[Mg]{Et_2O} R-MgX & \text{(1)} \\
R-MgX + \text{ketone} & \rightarrow R-OH & \text{(2)}
\end{align*}
\]
Addition Funnels

◦ Like a separatory funnel, but with ground glass at the bottom. ($$$)

◦ Allows slow addition of one reagent to another:
  ◦ control of heat generation (if an exothermic reaction)
  ◦ control of reagent concentration

◦ Add 2–3 mL of PhBr solution to the Mg. Stir until the reaction starts.

◦ Once the reaction begins, dribble rest of solution in over 5 min.
Procedure Notes

◦ Assemble glassware **before** it cools.
  ◦ Have Mg, drying tubes, condensor, clamps, and grease all set to go before you take your flask from the oven.
  ◦ Important to grease joints *lightly* before assembling, so joints do not freeze as the glass cools and contracts.

◦ Many alkyl halides are *lachyrmutations* (tear-gasses).
  ◦ Keep the halide and all glassware that contacted it in the hood.
  ◦ Rinse the residue in grad cylinder into the reaction with Et₂O.

◦ Once the Grignard Reagent has begun to form, the reaction should keep going on its own. If the reaction slows you may need to add a little heat to continue the reflux.

◦ Use your time wisely — the lab will end after 3 hours whether you are done or not.
Procedure Notes

- Most of the Mg will dissolve during the reaction. Any remaining Mg will dissolve in the work-up.
- Ether is highly flammable.
  - Do not turn hotplates on high.
  - No sparks or open flames.
- Two kinds of ether this week (anhydrous and work-up).
- Keep all layers during the extraction until you are certain you have recovered your product.
- End of first lab session: NMR and IR spectra of crude product. IR spectrum may be obtained outside of lab.
- Store your product in a tared vial in your drawer between the first and second week.
Cleanup

- Save desiccant for re-use
  - blue = good (save)
  - purple = going bad (dump)
  - red = dead (why didn’t this get dumped earlier?)

- Wipe the grease off all joints
  - grease + scrub-brush = globby mess
  - grease + oven = burnt on grossness
  - someone else’s grease is gross

- Wash and put in oven for next lab section:
  - rb flask
  - addition funnel
  - Claisen-head

- Do not wash:
  - graduated cylinder
  - condenser
  - drying tubes
Vacuum Distillation

Second Week:
- Vacuum distillation into a tared Hickman head
- NMR and IR spectra

Vacuum Distillation:
- Like regular distillation but done under vacuum
- Lowers BPs so that high-boiling compounds may be distilled
  - eg: in a pressure cooker, water boils $>100^\circ$
  - a 5-min egg takes 7 min to cook in Denver
- Be careful putting system under vacuum:
  - Bumping and Frothing are common:
    - Apply vacuum slowly
    - Stir vigorously while applying vacuum or heat
    - Do not apply vacuum if warm
    - Do not use low bp solvents (Et$_2$O, CH$_2$Cl$_2$) to transfer cpd into flask
- Check the vacuum before heating system
Formal Report

- See *Lab Manual* for instructions.
- Some things to remember:*
  - Your abstract should include what you did and how you know what you did.
  - Include all applicable steps in your reaction and mechanism.
  - All of your reagents should be in appropriate units.
  - Your experimental should be able to tell a chemist how to recreate your experiment. Do not mention extraneous glassware.
  - Format your NMR and IR correctly for your experimental.
  - In your discussion, explain how the NMR and IR spectra let you know what your product is.
  - Include your calculations.
  - Label and assign all of your spectra.

* This is not an exhaustive list of everything in your report. Use this along with your lab manual to guide you in the writing of your report.