The Synthesis of Triphenylmethanol

In this laboratory exercise we will synthesize Triphenylmethanol, a white crystalline aromatic compound.

\[
\begin{align*}
\text{HO} & \quad \text{phenyl} \\
\text{phenyl} & \quad \text{phenyl} \\
\end{align*}
\]

Triphenylmethanol is in and of itself not very important as an end product, but the synthetic route used to produce it is extremely important. This route involves the production of a Grignard Reagent, which is used to generate needed Carbon-Carbon bonds in the product. This is extremely important because synthetic methods for assembling Carbon-Carbon bonds are few and far between.

In 1912, Victor Grignard received the Nobel Prize in chemistry for his work on the reaction that bears his name, a Carbon-Carbon bond-forming reaction by which almost any alcohol may be formed from appropriate alkyl halides and carbonyl compounds. The Grignard Reagent is easily formed by reaction of an alkyl halide (R-X), in particular a Bromide, with Magnesium Metal in anhydrous Diethyl Ether or Tetrahydrofuran (THF). Although the reaction can be written and thought of as simply:

\[
R\text{-Br} + \text{Mg} \rightarrow R\text{-Mg-Br}
\]

it appears that the structure of the Reagent is much more complex. There is evidence that at low concentrations the Reagent exits as Dialkylmagnesium complexed to the Ether solvent in a four-coordination complex:

\[
2 \text{R-Mg-Br} \rightleftharpoons \text{R-Mg-R} + \text{Br-Mg-Br}
\]
At higher concentrations these monomers dimerize via bridging Bromide Ions:

\[
\begin{align*}
\text{R} & \quad \text{Mg} \quad \text{Br} \\
\text{(CH}_2\text{CH}_2\text{)}_2\text{O} & \quad \text{Mg} \quad \text{Br} \\
\text{O(CH}_2\text{CH}_2\text{)}_2 & 
\end{align*}
\]

The Grignard reagent is a strong base and a strong nucleophile. As a base, it will react with all protons that are more acidic than those found on alkenes and alkanes. Thus Grignard reagents react readily with Water, alcohols, amines, thiols, etc., to generate an alkane:

\[
\text{R-Mg-Br} + \text{H}_2\text{O} \quad \rightarrow \quad \text{R-H} + \text{HO-Mg-Br}
\]

Thus, once prepared, the Grignard Reagent must be kept extremely dry.

Because of the extreme polarization of the Carbon-Metal bond in the Reagent, the Carbon behaves as a Carbanion and thus is strongly nucleophilic.

\[
\text{C}^- \quad \text{Mg}^+
\]

As a nucleophile, the carbanion will readily react with carbonyl compounds to form an alkoxide ion. The alkoxide ion, as a strong base, can be readily protonated to form the corresponding alcohol.

To generate the Reagent, Magneisum Metal and the halide are added to dry ether or THF. Because the metal has a coat of oxide on the outside, some crushing is required to expose a fresh surface. Reaction will begin at the exposed surface, as evidenced by a slight turbidity in the solution and evolution of bubbles. Once the exothermic reaction starts, it proceeds easily, the Magnesium dissolves, and a solution of the Grignard Reagent is formed. (The solution is often turbid and gray due to impurities in the Magnesium.) The Reagent is not isolated but reacted immediately with an appropriate carbonyl compound.

The great versatility of this reaction lies in the wide range of reactants that undergo reaction with the Grignard Reagent.
For the present experiment, we will synthesize a tertiary alcohol; Triphenylmethanol. This can be accomplished by generating a Grignard Reagent from an aryl halide, Bromobenzene, and then treating it with either Benzophenone or Methyl Benzoate.

\[
\text{Bromobenzene} + \text{Benzophenone} \xrightarrow{1. \text{Mg, THF}} \text{MgBr} \xrightarrow{2. \text{H}_3\text{O}^+} \text{Triphenylmethanol}
\]

In the first reaction, the Grignard Reagent is added to the electrophilic center of the carbonyl compound, Benzophenone, to form the intermediate magnesium alkoxide. Treatment with acidified ice water will liberate the tertiary alcohol product, Triphenylmethanol.

\[
\text{Bromobenzene} + 2\text{Methyl benzoate} \xrightarrow{1. \text{Mg, THF}} 2\text{MgBr} \xrightarrow{2. \text{H}_3\text{O}^+} 2\text{Triphenylmethanol}
\]

In the second reaction, one equivalent of the Grignard Reagent is added to the electrophilic center of the carbonyl compound, Methyl Benzoate, to form Benzophenone. However, Benzophenone is more reactive than Methyl Benzoate and immediately reacts with a second equivalent of Grignard Reagent. In order to produce Triphenylmethanol, two equivalents of the Grignard Reagent are required to react with the ester.
The primary impurity present as a result of using this methodology is Biphenyl; formed by reaction of Phenylmagnesium Bromide with unreacted Bromobenzene.

An effective way to lessen this side reaction is to add the Bromobenzene to the reaction mixture slowly. Thus, it will immediately react with the Magnesium and not be present in high enough concentrations to react with previously formed Grignard Reagent.
Pre-Lab Questions

1. How much (in mmoles) is 2 g of Magnesium?

2. How much (in mmoles) is 8 mL of Bromobenzene?

3. How much Methyl Benzoate OR Benzophenone is needed to completely react with the resulting Grignard Reagent? (Hint: Which of the above is the limiting reagent for this reaction?)
Procedure

All equipment (a) a 100-mL reaction flask, (b) a magnetic stir bar, (c) a condenser, (d) two 50-mL Erlenmeyer flasks, and (e) a 100-mL graduated cylinder must be absolutely dry, preferably over the last week. Dry THF is readily available from a solvent drying still in the hood.

Place a 250-mL beaker half-full with water to warm (45-50 °C) on the hot plate.

Generate the Grignard Reagent

The Grignard Reagent is prepared in a dry 100-mL reaction flask fitted with a long reflux condenser. A Calcium Chloride drying tube inserted in a cork that will fit either the flask or the top of the condenser is also made ready.

Assemble the reaction flask containing the magnetic stir bar with the condenser and drying tube. Allow the set-up to cool to room temperature. The flask on cooling pulls dry air through the calcium chloride.

Weigh out 2.5 g of Magnesium turnings. Crush with a pestle in a mortar to break up some of the Oxide coating and expose some fresh metal surface. Add this to the 100-mL reaction flask. Follow with 10 mL of THF. Add 1.8 mL of Ethylene Bromide to the reaction mixture. (The Ethylene Bromide assists in generating the Reagent.) Boil the solution using the hot water bath for 15 minutes

Prepare, in a 50-mL Erlenmeyer flask, a solution containing 8 mL of bromobenzene in 15 mL of THF.

NOTE: Have an ice-water bath on hand. Formation of the Grignard Reagent is exothermic. Your TA will direct and assist you in the generation of the Grignard Reagent.

Now, add the Bromobenzene solution dropwise, via a dropping funnel, to the reaction flask at the rate of about 2 drops per second. The solution should soon turn colorless but cloudy. Maintain moderate reflux with intermediate heating and cooling (raise the reaction flask out of the warm water bath and, if needed, into the ice-water bath). If the reaction is occurring too vigorous, raise the set-up out of the warm water bath, allow the reaction to cool and subside. Add an additional 5 mL of THF if needed.
After all the Bromobenzene has been added and the reaction stops refluxing spontaneously, heat the reaction mixture for 15 minutes to ensure complete formation of the Grignard Reagent.

**Add the Carbonyl Compound (Methyl benzoate or Benzophenone)**

While the Grignard Reagent is processing, prepare the solution of carbonyl compound in the same 50-mL Erlenmeyer flask with 15 mL of dry THF.

Cool the reaction mixture for several minutes. Add the solution of carbonyl compound dropwise to the Reagent mixture. After addition of 5 mL of solution, place the reaction flask back in the water bath to begin warming again. Continue adding the solution of carbonyl compound. When addition is complete, rinse the 50-mL Erlenmeyer flask with 5 mL of THF and add. Reflux for another 15-20 minutes.

**Quench the Grignard Reaction**

Cool the reaction mixture. Place 25 mL of 1 M Sulfuric Acid and 25 g of Ice in a 250-mL beaker. Set aside 10-20 mL of this cold aqueous acid solution. Pour the reaction mixture into the 250-mL beaker. Rinse the reaction flask with the reserve aqueous acid solution and pour into the beaker. Stir the mixture until the salts and bits of unreacted Magnesium dissolve.

**Isolation the Crude Triphenylmethanol**

While the mixture is allowed to stir, set up for an extraction using a 125-mL separatory funnel. Filter the solution through a cotton-plugged funnel into the separatory funnel. Shake, vent, and separate the layers. Then proceed as directed:

1. Return the aqueous layer and extract with 50 mL of ether,
2. Wash the combined organic layer in succession with 25 mL of Water, 25 mL saturated aqueous Sodium Bicarbonate solution, and 25 mL of saturated aqueous Sodium Chloride solution.
3. Dry the organic layer over a Sodium Sulfate.

Filter the solution through another cotton-plugged funnel into a 125-mL Erlenmeyer flask. This is a good stopping point.

Add 20 mL of Ligroin or Hexanes and set on a hot plate to slowly concentrate. Concentration allows for the crystallization of Triphenylmethanol from the mixed solvents. When crystallization begins, remove from the hot plate and allow the solution to cool to room temperature then to 0 °C.

Collect the first crop of Triphenylmethanol by vacuum filtration using a Hirsch or Büchner funnel. Weigh the dry product. Check the melting point to determine whether a recrystallization is needed.
A second crop could be obtained by concentrating the mother liquor.

**Recrystallization of the Crude Triphenylmethanol**

After checking the melting points of all crops, determine if recrystallization is needed.

Recrystallization of Triphenylmethanol can be accomplished by dissolve the crude material in hot Dichloromethane and adding four times the volume of Hexanes. Heat to dissolve and allow to cool. Collect by vacuum filtration and determine yields.

Determine the Percentage Yield of your product.
Post Lab Questions

1. In a similar Grignard reaction to the one you performed, provide the reactants needed to synthesis the following tertiary alcohol. (There are more than one possible set of reactants.) Put the reactant(s) and product(s) into a synthetic equation.

   ![Chemical Structure]

   The carbocation formed from this tertiary alcohol is called Malachite Green.

2. Provide a mechanism for the tertiary alcohol of Question 1. Use your chosen reactants.