

CH246 Exp 2: Grignard Reaction

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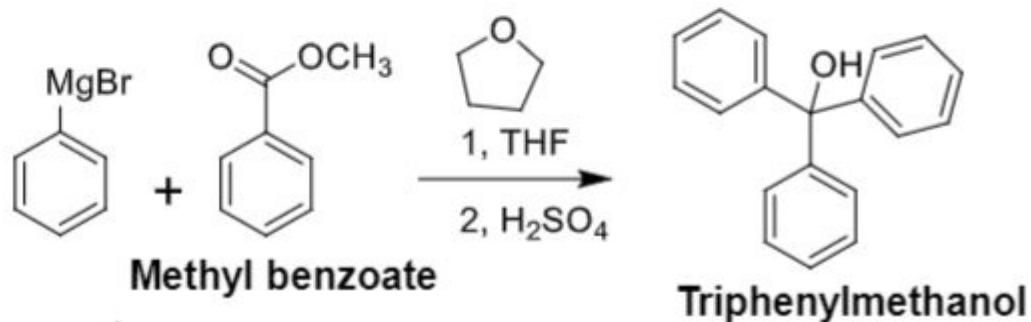
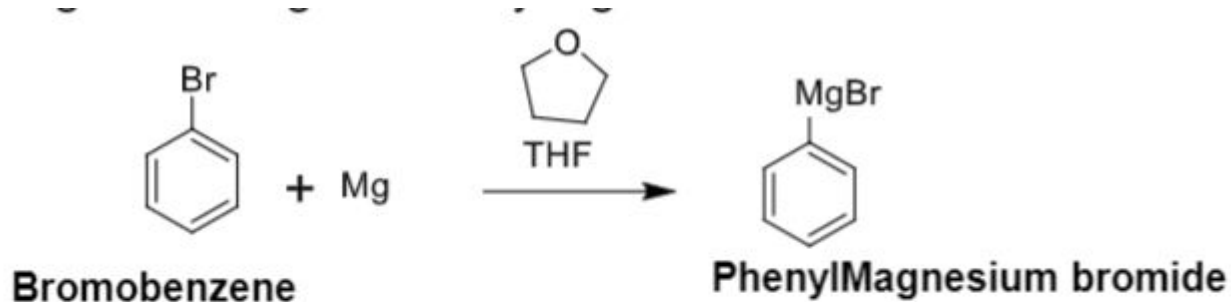
I pledge my honor that I have abided by the Stevens Honor System.

2/22/21

Purpose

The purpose of the lab was to learn the preparation procedure of creating a Grignard reagent of phenylmagnesium bromide from bromobenzene and magnesium and the synthesis of triphenylmethanol from methyl benzoate and the created Grignard reagent through a Grignard reaction.

Structures and Reaction



Reagents and Major Products

Name	M.W.	Density	Amount	Moles	Hazards	Role of Reagent
Bromobenzene	157.02 g/mol	1.5 g/cm ³	6.3 g	0.04012 moles	Flammable liquid and vapor; skin irritant; BP: 156 degrees C	reactant
Magnesium Turnings	24.305 g/mol	1.738 g/cm ³	1 g	0.04114 moles	Flammable solid; BP: 650 degrees C	reactant
Methyl benzoate	136.15 g/mol	1.088 g/cm ³	2.8 g	0.02057 moles	Combustible liquid; BP: 199 degrees C	reactant
Sulfuric acid	98.079 g/mol	1.840 g/cm ³	1.5mL	0.02814 moles	Corrosive; respiratory irritant; organ toxicity; BP: 337 degrees C	catalyst
THF	72.11 g/mol	0.809 g/cm ³	25mL	0.28047 moles	Flammable, toxic, hygroscopic; BP: 66 degrees C	Solvent
Sodium bicarbonate	84.001 g/mol	1.1 g/cm ³	10mL	0.13094 moles	Eye and skin irritant; toxic; BP: 851 degrees C	reactant
2-propanol	60.1 g/mol	0.785 g/cm ³	7mL per g of product		Flammable; respiratory and eye irritant; BP: 82.5 degrees C	reactant
Triphenylmethanol	260.33 g/mol	1.2 g/cm ³			Eye, skin, respiratory tract, and digestive tract irritant; BP: 360 degrees C	Product

Limiting Reagent

The limiting reagent is bromobenzene.

6.3 grams is used.

$6.3\text{g}/157.02\text{g/mol} = 0.04012$ moles of bromobenzene

Two moles of bromobenzene are required for 1 mole of product.

$0.04012 * \frac{1}{2} = 0.02006$ moles of triphenylmethanol

$0.02006 \text{ moles} * 260.33 \text{ g/mol} = 5.22$ grams of triphenylmethanol

Procedure Part 1

1. Place about 1 g of magnesium turnings and 1-2 small crystals of iodine into 100 mL round bottom flask. Assemble the apparatus as shown on the demonstration table. *Do not circulate the water in the condenser yet.* Heat the flask until you see pink or purple color in the flask. **Let it cool to room temperature.** (This will drive off any moisture in the air).
2. In the meantime, prepare a solution of 4.2 mL (6.3 g) of bromobenzene in 15 mL of tetrahydrofuran (THF) and place in a DRY, stoppered Erlenmeyer or 50 mL round bottom flask. **Start water circulation in the condenser.**
3. Add about 5 mL of the solution (from step 2) to the reaction flask through Claisen side arm, stopper and stir gently. **(HAVE AN ICE BATH HANDY!).** A spontaneous reaction should occur as shown by the generation of heat and clouding of the contents of the flask. *If the reaction does not start spontaneously, warm the flask gently and/or add another crystal of iodine.*
4. After the initial reaction has subsided, add the remaining solution in portions, at a rate sufficient to maintain a gentle reflux (**Do not heat if not necessary**). **KEEP THE CLAISEN ADAPTER STOPPERED BETWEEN ADDITIONS.**
5. When all the bromobenzene solution has been added, heat the flask to gentle reflux for 15-20 minutes (most of the magnesium will have dissolved).
6. While the reaction mixture is refluxing, prepare a solution of 2.8 g of methyl benzoate in 10 mL of THF.
7. After the Grignard reagent is formed (step 6, after reflux), gradually start adding the methyl benzoate solution to the reaction mixture **while it is still warm (but not refluxing)**. A reaction should be apparent (heat will be produced). The methyl benzoate solution should be added slowly and in portions over a 10 minute period, stirring gently but with NO HEAT.

Procedure Part 1

- 8.. After addition is complete, let the reaction mixture stand at room temperature for about 15-20 minutes.
9. Cool the reaction mixture over ice and then pour it slowly with swirling into a 250 mL beaker which contains about 25 g crushed ice, 10 mL of cold water and 1.5 mL of sulfuric acid.
10. Leave the unreacted magnesium behind but transfer the reaction mixture with the rest of the solids (a little magnesium transferred won't hurt) to another beaker. Mix well and warm to room temperature. (This is to hydrolyze the magnesium salt).
11. Cover the beaker tightly with parafilm (no holes) and store in drawer until the next laboratory period.

Procedure Part 2

1. Take out the beaker containing reaction mixture from the drawer.
2. If most of the THF has evaporated during this time, add another 20 mL of EtOAc. Mix the contents well by swirling or stirring.
3. Take little bit of the top layer solution in a vial.
4. Take TLC of the pure methyl benzoate, pure triphenylmethanol and your solution from step 3. (Use 80% hexane/20% ethyl acetate mixture for development)
5. Decant the mixture from the magnesium (if any) into separatory funnel.
6. Wash with 2 x 10 mL water and 1 x 10 mL of 10% sodium bicarbonate solution. Each time save the top layer (EtOAc layer).
7. Pour the organic layer into a 50 mL Erlenmeyer flask and add 0.1 g of Magnesium sulfate (drying agent). Let it stand for few minutes and swirl occasionally.
8. Filter the solid using gravity filter into a 50 mL round bottom flask.
9. Rotavape the liquid (with help from TA).
10. Recrystallize compound from 2-propanol (7 mL of 2-propanol/ g of the product) or purify using CombiFlash separation system.
11. Weigh the dry product, record yield, % yield and TLC picture.
12. We will run the IR for few samples next week.

Part 1

Stepwise Procedure

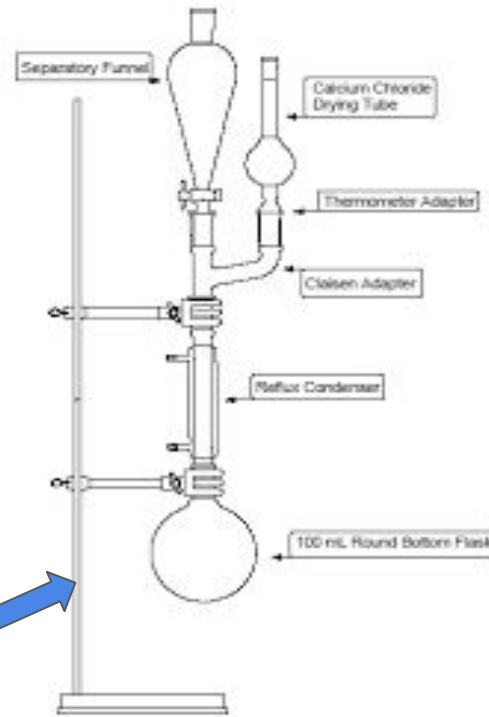
1. Place about 1 g of magnesium turnings and 1-2 small crystals of iodine into 100 mL round bottom flask. Assemble the apparatus as shown on the demonstration table. *Do not circulate the water in the condenser yet.* Heat the flask until you see pink or purple color in the flask. **Let it cool to room temperature.** (This will drive off any moisture in the air).



Assemble apparatus

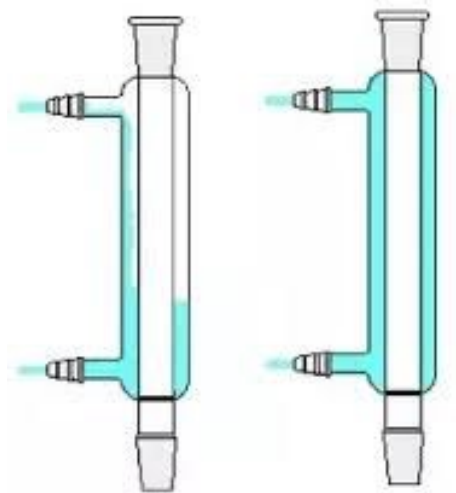
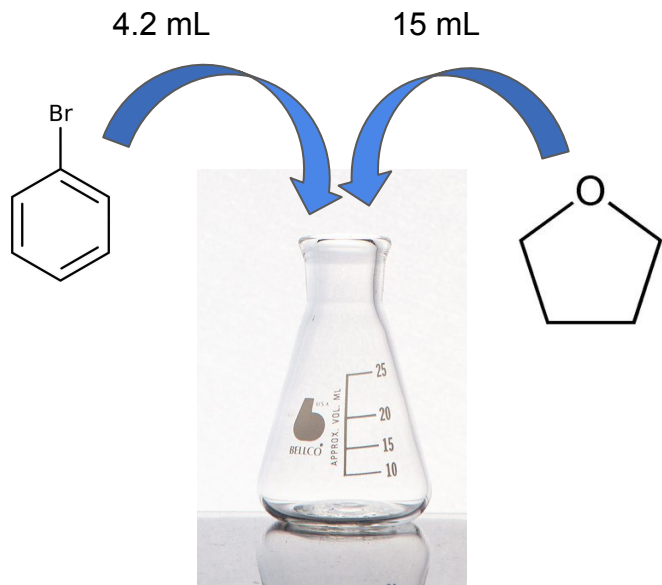


Heat flask to drive off any moisture



Stepwise Procedure

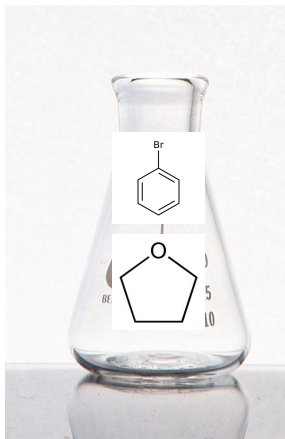
2. In the meantime, prepare a solution of 4.2 mL (6.3 g) of bromobenzene in 15 mL of tetrahydrofuran (THF) and place in a DRY, stoppered Erlenmeyer or 50 mL round bottom flask. **Start water circulation in the condenser.**



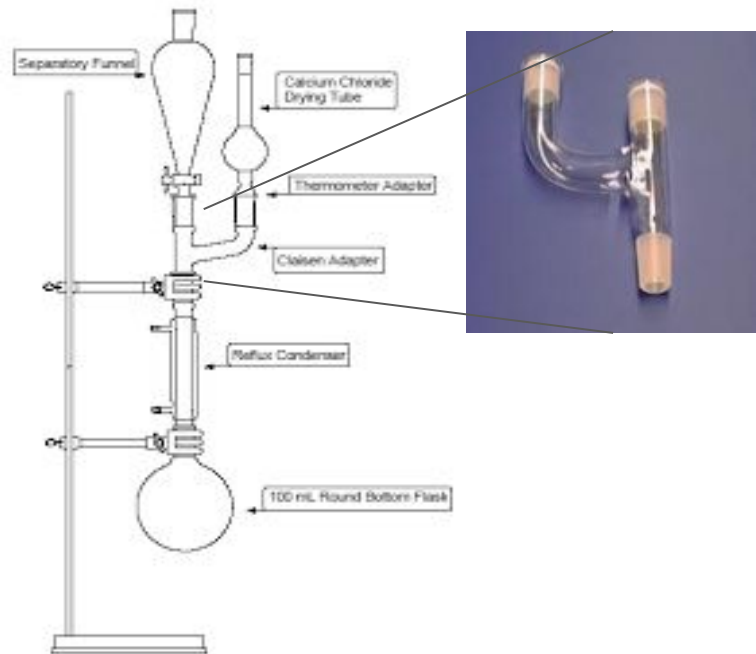
Start water circulation
in condenser

Stepwise Procedure

3. Add about 5 mL of the solution (from step 2) to the reaction flask through Claisen side arm, stopper and stir gently. **(HAVE AN ICE BATH HANDY!)**. A spontaneous reaction should occur as shown by the generation of heat and clouding of the contents of the flask. *If the reaction does not start spontaneously, warm the flask gently and/or add another crystal of iodine.*



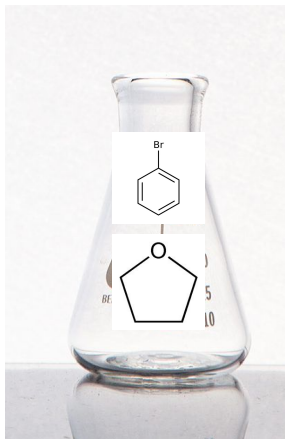
Add the mixture of bromobenzene and THF to the reaction flask with the Mg through the Claisen side arm



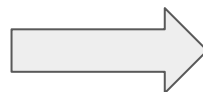
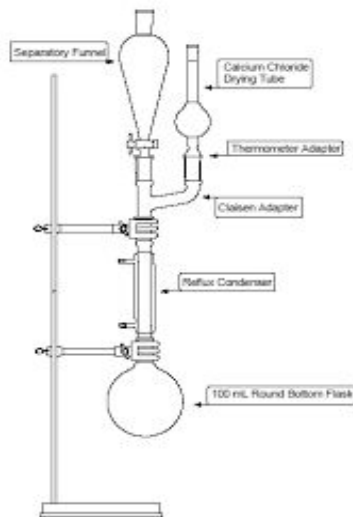
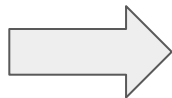
Stepwise Procedure

4. After the initial reaction has subsided, add the remaining solution in portions, at a rate sufficient to maintain a gentle reflux (*Do not heat if not necessary*). KEEP THE CLAISEN ADAPTER STOPPERED BETWEEN ADDITIONS.

5. When all the bromobenzene solution has been added, heat the flask to gentle reflux for 15-20 minutes (most of the magnesium will have dissolved).



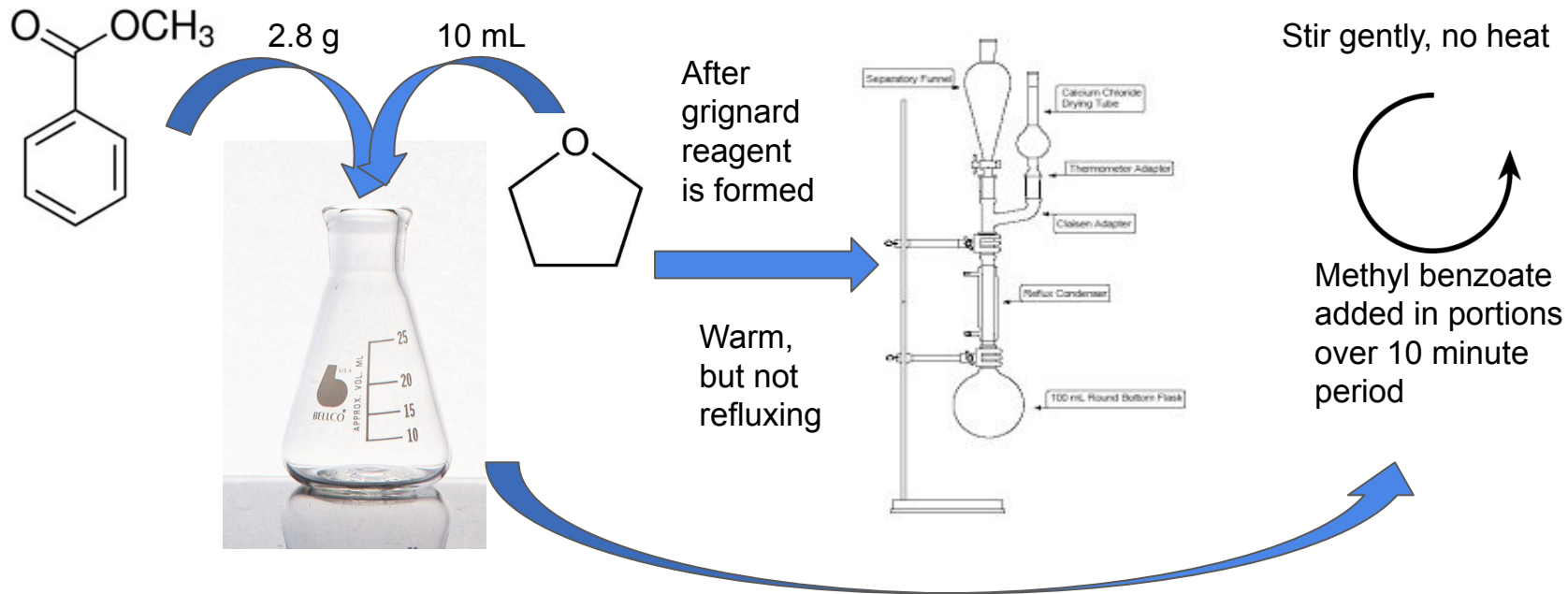
Continue adding solution to reaction in small intervals



Gently heat the flask to reflux after all the bromobenzene has been added

Stepwise Procedure

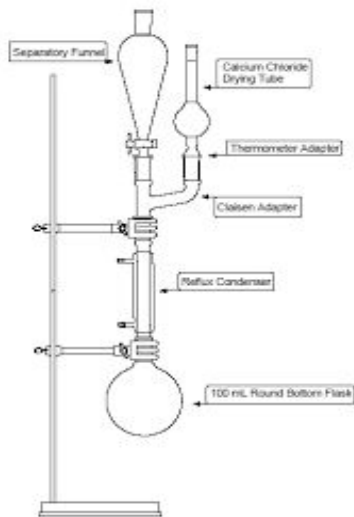
6. While the reaction mixture is refluxing, prepare a solution of 2.8 g of methyl benzoate in 10 mL of THF.
7. After the Grignard reagent is formed (step 6, after reflux), gradually start adding the methyl benzoate solution to the reaction mixture **while it is still warm (but not refluxing)**. A reaction should be apparent (heat will be produced). The methyl benzoate solution should be added slowly and in portions over a 10 minute period, stirring gently but with NO HEAT.



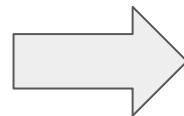
Stepwise Procedure

8. After addition is complete, let the reaction mixture stand at room temperature for about 15-20 minutes.

9. Cool the reaction mixture over ice and then pour it slowly with swirling into a 250 mL beaker which contains about 25 g crushed ice, 10 mL of cold water and 1.5 mL of sulfuric acid.



Cool reaction over ice

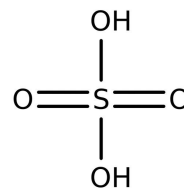


Add to beaker with the following:



25g of ice

10mL of water



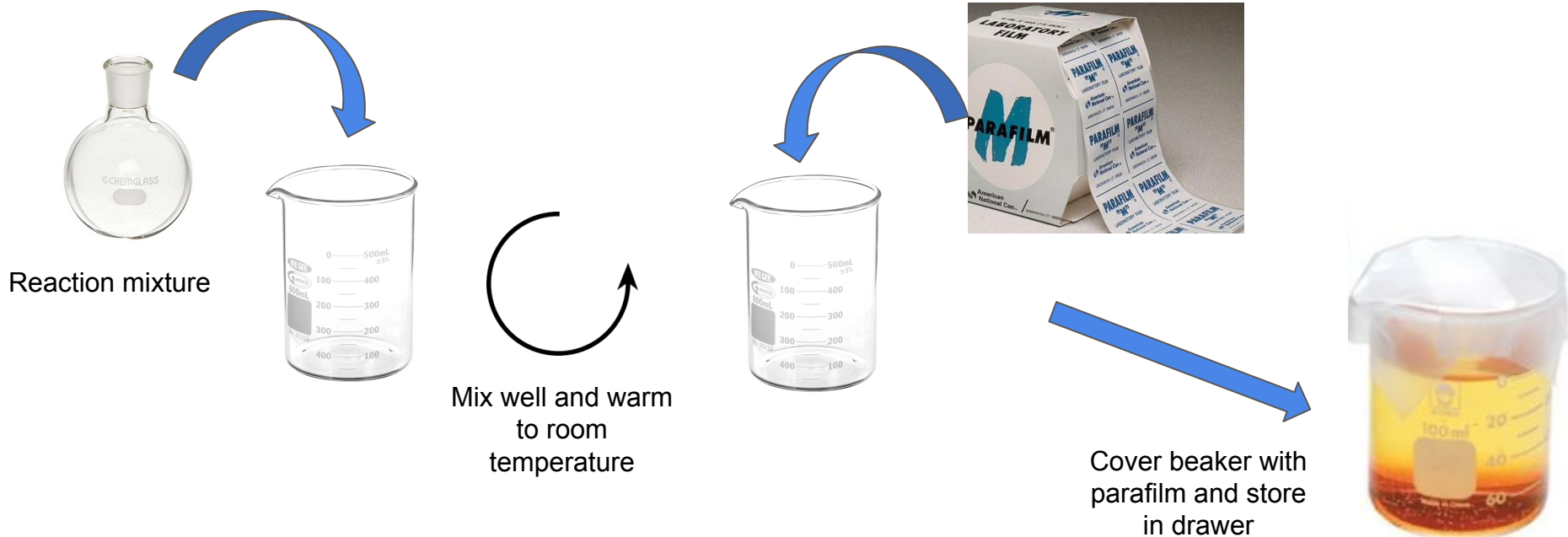
1.5 mL Sulfuric Acid

Let reaction vessel cool at room temperature

Stepwise Procedure

10. Leave the unreacted magnesium behind but transfer the reaction mixture with the rest of the solids (a little magnesium transferred won't hurt) to another beaker. Mix well and warm to room temperature. (This is to hydrolyze the magnesium salt).

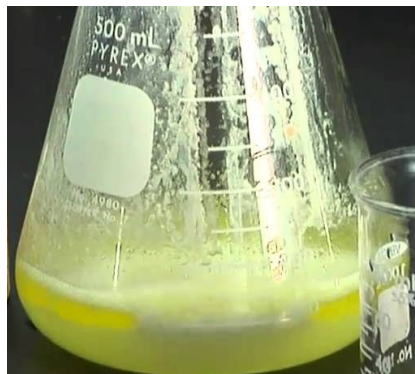
11. Cover the beaker tightly with parafilm (no holes) and store in drawer until the next laboratory period.



Part 2

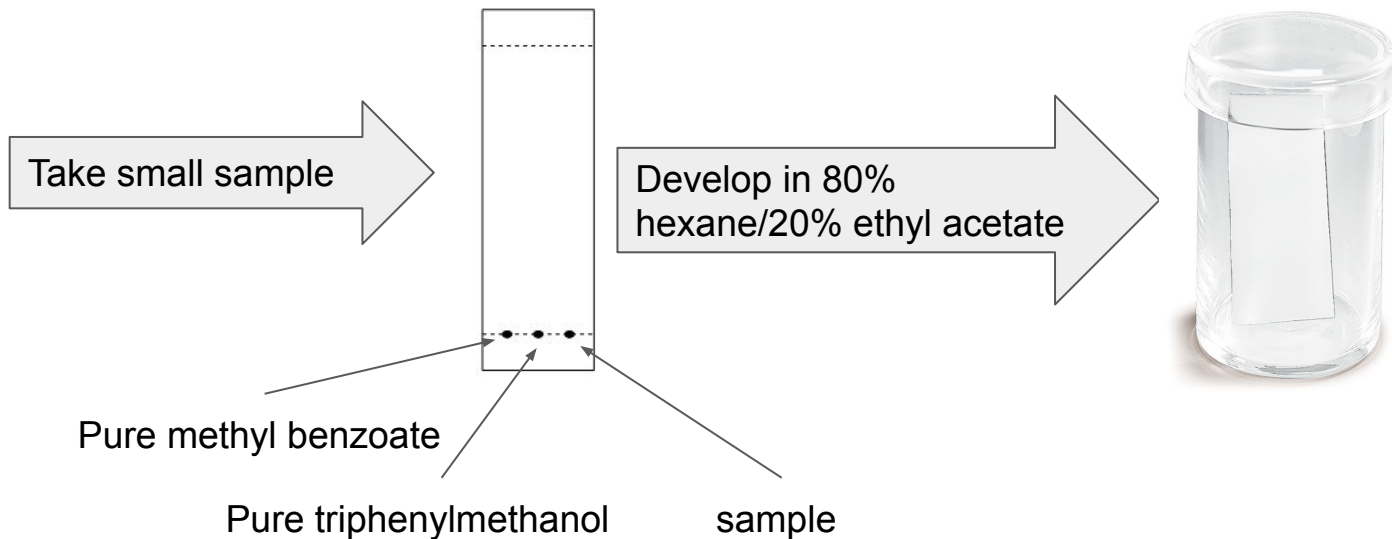
Stepwise Procedure

1. Take out the beaker containing reaction mixture from the drawer. If most of THF has evaporated, add another 10 mL of EtOAc.
2. Take a small sample of the top layer solution in a vial, and take a TLC of pure methyl benzoate, pure triphenylmethanol, and the sample. Use 80% hexane/20% ethyl acetate mixture for development.



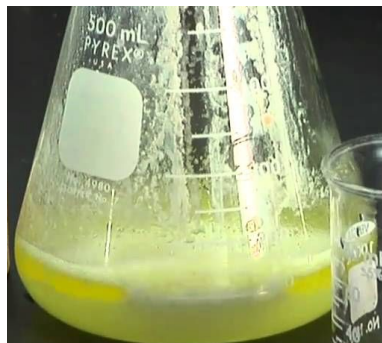
Reaction mixture

Add 10 mL EtOAc if necessary!

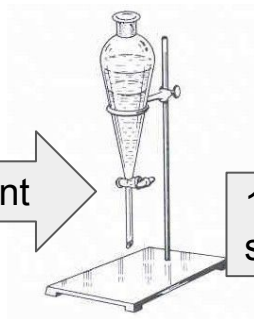


Stepwise Procedure (cont.)

3. Decant mixture from magnesium into separatory funnel.
4. Wash with 2 x 10 mL water and 1 x 10 mL 10% sodium bicarbonate solution. Save the top layer each time, and remove and discard bottom layer.

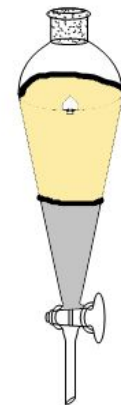


Decant



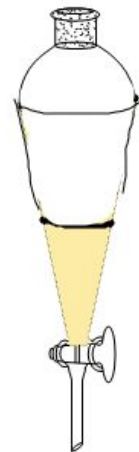
10 mL water,
shake and vent

Wash with water and then
bicarbonate to get rid of any
remaining excess sulfuric acid



Keep on ring stand

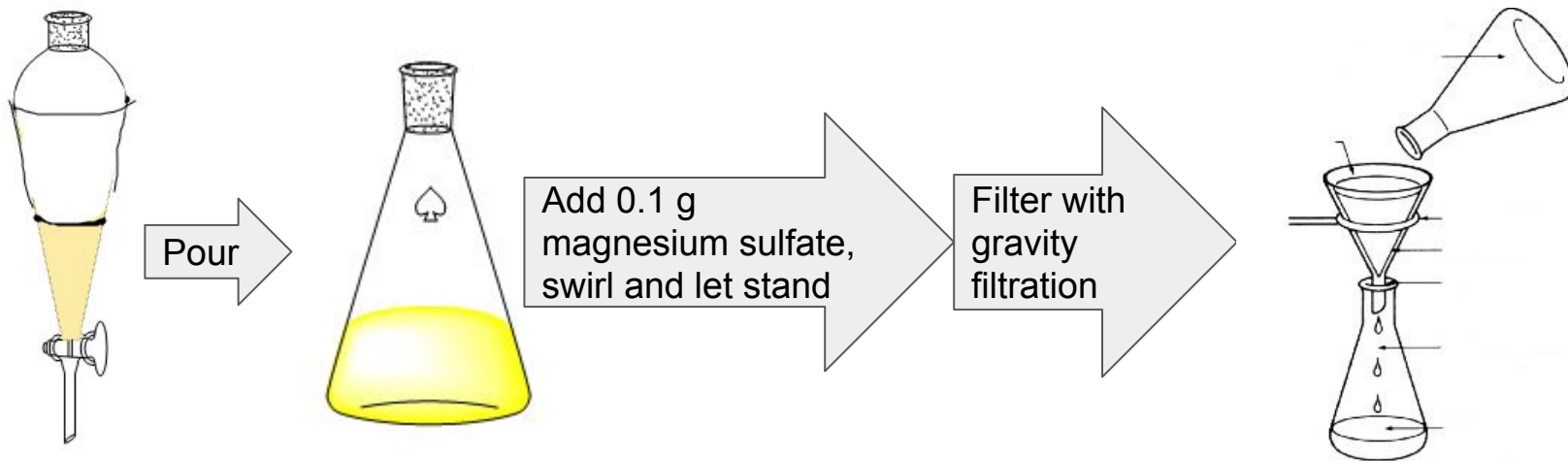
Remove
bottom layer



Repeat with 10 mL water and then 10 mL
10% sodium bicarbonate solution

Stepwise procedure (cont)

5. Pour organic layer into 50 mL Erlenmeyer flask and add 0.1 g of magnesium sulfate (drying agent). Let stand for a few minutes and swirl occasionally.
6. Filter the solid using gravity filtration into a 50 mL round bottom flask.

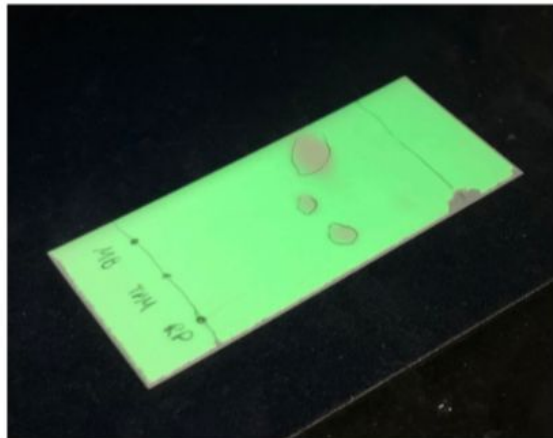


Stepwise Procedure (cont.)

7. Rotavape the liquid.
8. Recrystallize compound using 2-propanol (7 mL 2-propanol/1 g product).
9. Weigh dry product, record yield, % yield, and TLC from earlier.



Results (TLC Data)



Solvent: 80% hexane/20% ethyl acetate

Travel distance: 6.0 cm

Spot 1: Pure methylbenzoate

Travel distance: 4.2 cm

Rf: $4.2 \text{ cm} / 6.0 \text{ cm} = 0.7$

Spot 2: Pure triphenylmethanol

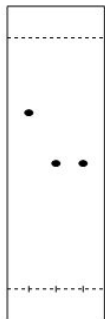
Travel distance: 3.0 cm

Rf: $3.0 \text{ cm} / 6.0 \text{ cm} = 0.5$

Spot 3: Reaction mixture

Travel distance: 3.0 cm

Rf: $3.0 \text{ cm} / 6.0 \text{ cm} = 0.5$



Results (% yield of crude and recrystallized product)

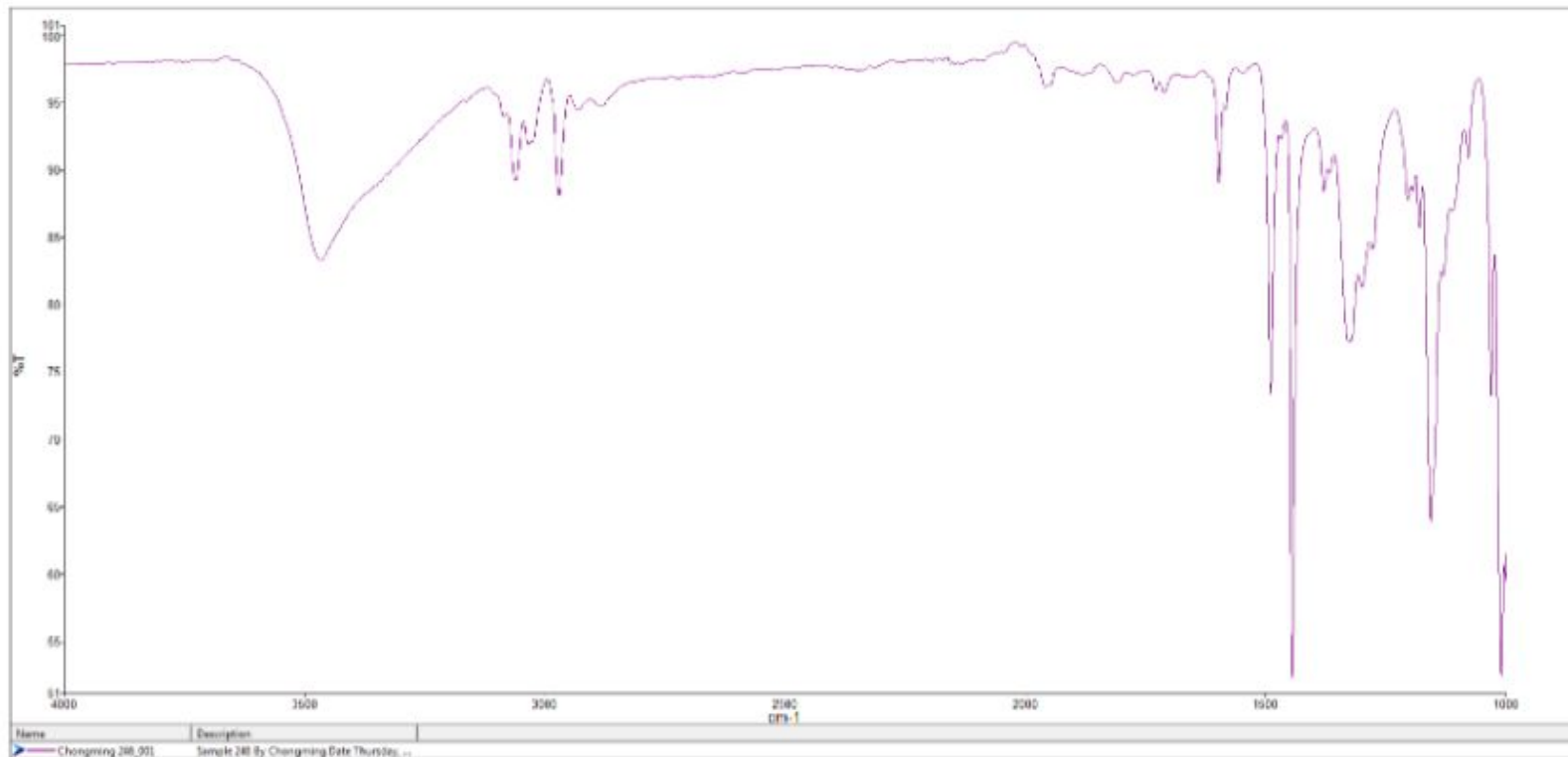
Theoretical yield = 5.2 g

$$\begin{aligned} & 6.3 \text{ g bromobenzene} * \frac{1 \text{ mol bromobenzene}}{157.01 \text{ g bromobenzene}} * \frac{1 \text{ mol phenylmagnesium bromide}}{1 \text{ mol bromobenzene}} \\ & * \frac{1 \text{ mol triphenyl methanol}}{2 \text{ mol phenylmagnesium bromide}} * \frac{260.32 \text{ g triphenyl methanol}}{1 \text{ mol triphenyl methanol}} \\ & = 5.2 \text{ g triphenyl methanol} \end{aligned}$$

Weight of crude product = 3.1 g -- % yield = 3.1 g / 5.2 g = 60%

Weight of recrystallized product = 2.2 g -- % yield = 2.2 g / 5.2 g = 42%

Results (IR of triphenylmethanol)



Conclusion

This lab demonstrated the preparation of a Grignard reagent and a Grignard reaction by using bromobenzene and magnesium to form phenylmagnesium bromide and combining that with methyl benzoate to undergo the Grignard reaction to form triphenylmethanol. This was accomplished, with the success being verified by the TLC results of the reaction sample, pure methyl benzoate, and pure triphenylmethanol. The triphenylmethanol, being more polar than methyl benzoate, has a lower R_f of 0.5, compared to 0.7. The obtained product matched the pure triphenylmethanol in both R_f and shape of the spot, affirming the success of the reaction. One important takeaway was the specific conditions Grignard reactions took place in, such as the absence of water and the slow controlled rate of reaction. Another takeaway was the workup from the reaction mixture to the final pure product using separation, washings, the rotavapor, and recrystallization. There were no issues during the experiment, and no future recommendations, due to the lab being conducted remotely. Practical applications of this reaction are for the synthesis of several important drugs and medicines for cancer treatment and other chronic diseases.

Postlab Questions

- 1. Most of you have a side product as a spot higher than methylbenzoate in the TLC. What could that side product be which comes higher than methylbenzoate in TLC?**

The side product that is higher must be a product that is less polar than methylbenzoate. This would not be the diphenylmethanol, as that also contains an OH group, so it is more polar. The side product is diphenyl, which could form during creation of the Grignard reagent, as the carbon on bromobenzene has a partial positive charge and the carbon on phenylmagnesium bromide has a partial negative charge, which can react to form diphenyl.

Postlab Questions (cont.)

2. Perform a Scifinder search and report a method to prepare triphenylmethanol from benzophenone. Attach screenshot of Scifinder results.

Reaction Structure structure variable only at spe... > reactions (75) > reaction 7 (of 75)

REACTION DETAIL ⓘ

Get Reference
Detail

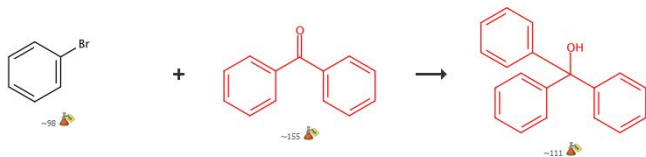
Get Similar
Reactions

Link to
Other Sources

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7. Single Step *Hover over any structure for more options.*



Overview

Stages

- 1.1 R: Mg, S: THF, 20 min, 45°C
- 1.2 S: THF, 10 min, 45°C; cooled
- 1.3 R: NH_4Cl , S: H_2O

Notes

ultrasound, Cup Horn (200 W, 300 kHz) ultrasound used, other ultrasound sources also used, Grignard reaction, Reactants: 2, Reagents: 2, Solvents: 2, Steps: 1, Stages: 3

Transformation:

1. Addition of Grignard/ Organometallic Reagents to Aldehydes and Ketones

Yield

98%

METHODSNow™

Procedure

1. Add 366 mg (15 mmol, 1.5 eq) of Mg chips, 3 mL of dry THF and 1 mmol (0.1 eq) of bromobenzene to a dry, one neck, round bottom flask.
2. Sonicate the mixture (water bath temperature: 55 ± 1 °C) under a nitrogen atmosphere until activation.

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