Friedel-Crafts Acylation

In this lab you will be synthesizing acetyl ferrocene from ferrocene via a Friedel-Crafts acylation. Friedel-Crafts acylation involves the addition of a keto group into an arene through the use of anhydride or acyl halide reagents with the help of a Lewis acid. While in principle the Lewis acid could be used catalytically, the Friedel-Crafts acylation often requires substantial amounts of the “catalyst”, usually stoichiometric amounts that can not to be recovered. In addition to this acylation methodology there is another form of Friedel-Crafts chemistry that you may be familiar with, Friedel-Crafts alkylation. It is imperative you make the distinction now that you are NOT alkylating ferrocene, adding saturated carbon chains, but rather are acylating, by introducing the ketone functional group to the ferrocene substrate. Alkylation tends to be less efficient than acylation due to the fact that polysubstitution is often observed. Acylation, once achieved, deactivates the product and polysubstitution becomes impossible. For this reason, it is not uncommon for research chemists to conduct Friedel-Crafts acylation when carbon chain addition is required, as the acylated product can be reduced fairly easily to yield the desired monosubstituted product (Scheme 1).

A Friedel-Crafts acylation or alkylation may be carried out intermolecularly, between two substrates, as seen in (Scheme 1), or intramolecularly where two functional groups on the same compound interact with one another (Scheme 2). When Friedel-Crafts chemistry is carried out in an intramolecular fashion, alkylation procedures serve as a suitable means for 5-, 6-, and even 7-membered ring formation.

In general, higher yields for acylation reactions are obtained from starting materials that are more electron rich. Similarly, when using acyl halide reagents, increased reactivity is achieved when the halogen in question is...
larger in size, i.e. I > Br > Cl > F.\(^1\) Inversely, it is worth noting that substrates baring unprotected Lewis basic functional groups, such as amines, will hinder arene acylation yields as substitution will preferentially occur on the heteroatom (Scheme 3).\(^1\)

![Scheme 3: Heteroatom more favorably acylated](image)

The reaction being conducted today will use an acid anhydride rather than an acyl halide. The anhydride allows this reaction to be carried out “neat,” without solvent, and will cut down on the amount of undesired by-products and waste.

**Synthesis of Acetylferrocene**

![Synthesis of Acetylferrocene](image)


**Data Table:** Have a copy of the reaction scheme, reference, data table and procedure in your notebook prior to the beginning of lab. Fill in the amount, mmol, and mole ratio of each substrate when you actually complete that portion of the experiment. Sections with a “-” do not need to be filled in or included in your report.

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<th>Ferrocene</th>
<th>Acetic Anhydride</th>
<th>85% Phosphoric Acid</th>
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**Procedure:**

Obtain a 250 mL beaker; fill it to the half way mark with water, and heat to near boiling (~ 90\(^0\) C). While you are waiting for your water bath to reach the appropriate temperature, place 100 mg of ferrocene into a 50.0 mL round bottom flask equipped with a magnetic stir bar and seal the flask with a rubber septum.
You now need to purge your round bottom flask of air and replace it with nitrogen. To do this, place one small needle through the top of your septum to create an opening between the environment and the inside of your flask. Next you will attach a second needle to the end of a nitrogen line that is equipped in each fume hood and allow a gentle stream of nitrogen to flow into your round bottom by piercing your rubber septum once again. As nitrogen flows into your round bottom air will be pushed out of the needle that is open to the environment. Allow nitrogen to flow for about one minute and then remove the needle that is not attached to the nitrogen line so nitrogen is no longer allowed to flow out of your flask.

With your round bottom now under a nitrogen atmosphere, place 2.00 mL of acetic anhydride carefully into your flask via a syringe. Do not allow the acid to splash your ferrocene onto the side of the flask. Next, place 0.4 mL of 85% phosphoric acid into your reaction, also being careful that you do not splash any of your ferrocene onto the side of your flask. In order to dissolve your ferrocene as best as possible you will need to hold your flask over a stir plate and allow the stir bar to gently mix your reaction before placing it into the water bath. Note: your nitrogen line should have never left your round bottom and a steady stream of nitrogen should still be flowing into your flask. Not all of your ferrocene will dissolve at room temperature, so only mix gently for ~ 1 minute.

Once you have finished mixing your reaction, place your flask into your water bath for 12 – 15 minutes. You will notice a tar like substance beginning to develop as your reaction is heated. After the 12 – 15 minute mark has finished, remove your flask from the water bath and remove your septum and nitrogen line in the fume hood.

Obtain a precut TLC plate from your TA and co-spot your reaction mixture next to a standard of ferrocene in a 80:20 solution of Hexanes:EtOAc. To make your ferrocene standard you will place a very small amount of ferrocene (no more than a spatula tips worth) into a vial and dilute with 1.0 mL of EtOAc. You will now spot this sample on the left-hand side of your TLC plate with a capillary tube and spot your reaction mixture on the right-hand side using the other end of your capillary tube. Place your TLC plate into your beaker filled with your 80:20 solution of hexanes and EtOAc and sketch your results in your notebook.

When you have finished taking a TLC of your product you need to neutralize your reaction so you may isolate your product. Place 10.0 mL of room temperature water into your reaction flask and swirl the contents to break up the tar-like substance as much as possible. Using a 6 N solution of NaOH slowly add 1.0 mL at a time to your reaction flask while swirling to insure adequate distribution of your base. Record the pH of your reaction after the addition of each mL and stop once you achieve a pH of 7 or 8.

Once a neutral pH has been achieved, the product must be purified by crystallization. Place your reaction vessel in a beaker filled with ice and water and allow your reaction to sit for ~ 5 minutes; over that time crystals will begin to develop. As you are waiting for your crystals to form you should set up your vacuum filtration apparatus in order to optimize your time.
Once the crystals have formed, cap your flask with a glass septum and shake the contents of your reaction flask vigorously to try and free any solids from the walls of your flask. With your vacuum filtration apparatus set up and running, pour your reaction through your funnel so that your crystals will collect and dry on your filter paper. If any solids remain in your flask you may use an additional 2 – 3 mL of cold water to attempt removal. Obtain a weight of the crystals collected and write down a percent yield in your notebooks. At this point in time you have the option of dissolving a small amount of crystals to once again assay purity via TLC. If you are not happy with the purity of your sample, perform an additional recrystallization.

After you are satisfied with your purity, obtain an IR of your product, and make a GC sample. Your TA will give you your GC spectrum at the next scheduled lab meeting.

**Notes To Students:**

This lab is serving as a midterm, and as a result you will NOT be permitted to pose questions to your TA or your peers during the experiment. Your TA will be allowed to answer any question about the lab up until 4:00 PM the day before your midterm begins. This means that if any e-mail or message is received with a timestamp of 4:00 PM or later the TA will NOT respond. TAs outside of the CHM 226 lab around the department will also be instructed that they are not allowed to answer any questions for this specific lab. If you feel the necessity to ask a question during the experiment that is contingent on you progressing, the TA may answer but will assess a 10% penalty.

Laboratory technique and preparedness is essential in organic chemistry, and the procedure outlined above was written in excruciating detail. If for some reason you need to restart the experiment as a result of procedural or careless error you will be permitted to, however, a -50% penalty will be imposed. Also note, in lieu of any pre/post lab questions you will be graded on your yield as well as purity. This is why it is important to be truly satisfied with your sample purity and conduct the extra recrystallization if necessary.

Any technique that you have not previously done in lab that is required for this experiment, i.e. purging your round bottom with nitrogen, you will not be held responsible for and the TA will show you how to complete this technique when necessary. Any technique that you HAVE completed previously, such as setting up a reaction and vacuum filtering, you will be held fully responsible for. It will be up to you to prepare before hand and outline how to complete any technique that you feel is not adequately described in this handout.