A Friedel-Crafts Alkylation

The Synthesis of 1,4-Di-tert-Butyl-2,5-Dimethoxybenzene

In this laboratory exercise we will synthesize the compound 1,4-di-tert-butyl-2,5-di-methoxybenzene. And while this particular compound is not that important, its method of preparation, the Friedel-Crafts Alkylation, is.

1,4-Di-tert-Butyl-2,5-Dimethoxybenzene

In 1877, Charles Friedel and James Crafts discovered that an alkyl halide reacts with benzene in the presence of an aluminum halide AlX₃ (X = Cl, Br).

Charles Friedel  

James M. Crafts  
The products of this reaction are the corresponding alkylbenzene and hydrogen halide (HCl or HBr). This reaction, which can be carried out in the presence of other Lewis acids catalysts, is called the **Friedel-Crafts alkylation** reaction.

\[
\text{AlCl}_3 + \text{HCl} \rightarrow \text{Cl}^- + \text{AlCl}_4^-
\]

Typical Lewis acids for the Friedel-Crafts reaction are BF$_3$, SbCl$_5$, FeCl$_3$, AlCl$_3$, and AlBr$_3$. More generally, the Friedel-Crafts alkylation is a type of Electrophilic Aromatic Substitution reaction.

- **Friedel-Crafts Alkylation of Benzene with Chloroethane**

The Friedel-Crafts reaction begins with coordination of the Lewis acid to the halogen of the alkyl halide (step 1, alkyl halide activation). This coordination places a partial positive charge on the carbon bearing the halogen, making it more electrophilic for the electrophilic attack (step 2, electrophilic attack). The loss of a proton from the ring-system re-establishes aromaticity, the driving force for the reaction (step 3).

**Step 1: Alkyl halide activation**

\[
RCH_2X + \text{AlCl}_3 \rightarrow RCH_2X^+ + \text{AlCl}_4^-
\]

**Step 2: Electrophilic attack**

\[
\text{AlCl}_3 + \text{H}_2\text{C}^+\text{Cl}_2^- \rightarrow \text{H}_2\text{C}^+\text{Cl}_2^- + \text{AlCl}_4^-
\]

**Step 3: Proton loss**

\[
\text{H}_2\text{C}^+\text{Cl}_2^- + \text{AlCl}_4^- \rightarrow \text{H}_2\text{C}^- + \text{AlCl}_3
\]
With secondary and tertiary halides, free carbocations are usually formed as intermediates; these species attack the benzene ring in an electrophilic manner.

The alkylation of benzene or substituted benzenes is accompanied by two important side reactions:

(1) *Polyalkylation* of the benzene system

(2) *Carbocation rearrangement*

Both side reactions can drop the yield of the desired products significantly and additionally lead to a mixture that can be difficult to separate. Because of these unwanted side reactions, the application of the Friedel-Crafts alkylation reaction in organic synthesis is limited.

On a more positive note, it is possible to carry-out a Friedel-Crafts alkylation with any carboxationic intermediate. This commonly includes protonation of an alkene with HF or treatment of an alcohol with a dehydrating agent such as H$_2$SO$_4$ or BF$_3$.

In this experiment we will carry out a Friedel-Crafts reaction between 1,4-dimethoxybenzene and *tert*-butyl alcohol to afford 1,4-di-*tert*-butyl-2,5-dimethoxybenzene.

\[
\begin{align*}
\text{OCH}_3 & \quad + \quad 2 \ (\text{CH}_3)_3\text{COH} \quad \overset{\text{H}_2\text{SO}_4}{\longrightarrow} \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{C(CH}_3)_3 \\
\end{align*}
\]

In this reaction, the electrophile is a carbocation, generated by treating a tertiary alcohol (((CH$_3$)$_3$C-OH) with a strong acid (H$_2$SO$_4$) as the dehydrating agent. The advantage of this method for generating the electrophile is that the tertiary butyl cation is a stable carbocation and does not rearrange.

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CH}_3
\end{align*}
\]

After the electrophilic cation has been formed, it will attack the benzene ring (see mechanism above). Also note that in this reaction our ring is dialkylated. Polyalkylation occurs because alkylation increases the nucleophilicity of the ring, increasing the reactivity of the system. However, alkylation does not proceed beyond dialkylation, in this case, because the two remaining positions on the ring are too sterically hindered for
further reactions to occur. Finally, note the alkylation occurs ortho to the methoxy (-OCH₃) groups present. This is because the methoxy group is an activating ortho-para director.

This type of reaction is commercially very important. If our reaction were carried out instead with 4-methylphenol as the aromatic system, 2,6-di-tert-butyl-4-methylphenol results. This compound is referred to industrially as BHT (butylated hydroxytoluene) and is a food additive which prevents oxidative spoilage.
Pre-Lab Questions

1. Write a mechanism for the formation of (1,1-dimethylethyl)benzene from 2-chloro-2-methylpropane (tert-butyl chloride), benzene, and catalytic AlCl₃.

2. In the experiment described above tert-butyl alcohol is used in the alkylation of 1,4-dimethoxybenzene. Which product(s) would be formed if n-butyl alcohol was used instead?

3. Would it be possible to obtain 1,4-di-tert-butyl-2,5-dimethoxybenzene by treating 1,4-dimethoxybenzene with methyl propene and sulfuric acid? Why?

4. In 2003, more than 7 billion pounds (3.1 billion kilograms) of (1-methyl-ethyl)benzene, an important industrial intermediate in the manufacturing process of phenol, was synthesized in the Unites States from propene and benzene in the presence of phosphoric acid. Write a mechanism for the formation of (1-methyl-ethyl)benzene in this reaction.
Procedure

**Precautions**  Wear gloves when handling either concentrated or fuming sulfuric acid. The latter should be poured only in a fume hood. Acetic acid is not as strongly acidic as sulfuric acid but should be handled very carefully. Make certain that a supply of solid sodium carbonate or sodium bicarbonate is available to be spread on acid spills.

**Hazards**  Acetic and sulfuric acid are dehydrating agents which can cause severe burns. Fuming sulfuric acid poses the same danger and contains the irritating gas SO_3_. Avoid contact or inhalation.

1. **In a fume** hood, charge a 50 mL Erlenmeyer flask with 1.5 g 1,4-dimethoxybenzene, 2.5 mL tert-butyl alcohol, and 5 mL glacial acid. Swirl briefly to mix the contents and then clamp the neck of the flask and immerse it in an ice-water bath and let it cool.

2. Measure 2.5 mL concentrated sulfuric acid in a graduated cylinder (gloves) and pour it into a 50 mL flask. Measure 2.5 mL fuming sulfuric acid in a graduated cylinder (gloves, fume hood) and add it to the sulfuric acid. Place this flask in the ice bath.

3. Holding the first flask by the clamp, swirl the flask in the ice bath until the internal temperature (thermometer) is about 0°C. Leaving the flask in the ice bath, clamp it to the ring stand.

4. Using a second clamp, fix a small separatory funnel so the delivery tube is in the neck of the clamped flask.

5. Transfer the cold sulfuric acid to the separatory funnel and add the acid dropwise during about 5 min. While adding the acid, loosen the clamp where it attaches to the ring stand just enough so the flask can be gently rocked from side to side. Agitate the flask gently during the acid addition.

6. After the addition is complete, stir the slurry briefly. Note the temperature, which should be near 25°C, and swirl the flask for an additional 5 to 10 min.

7. Add about 6 g crushed ice and then add enough water so that the flask is nearly full but may still be swirled. Filter the reaction mixture (Buchner funnel) using gentle suction.

8. Wash the filter cake with three 8 mL portions of cold distilled water. Turn on the suction full force and place a second piece of filter paper on the solid. Press down on the filter paper with the top of a cork to press out residual water.
9. Remove the filter paper and wash the product with three 5 mL portions of ice-cold methanol.

10. Gently scrape the solid into a dry 50 mL Erlenmeyer flask and dissolve the solid in 6 mL dichloromethane.

11. Add sodium sulfate or magnesium sulfate to dry the solution and stir for 10 min. Gravity filter into a second 50 mL Erlenmeyer flask to remove the drying agent and evaporate the dichloromethane using a rotary evaporator.

12. Recrystallization of the crude product from 5 to 7 mL ethanol yields 1 to 2 g 1,4-di-tert-butyl-2,5-dimethoxybenzene as white plates, mp 104 to 105°C.

**Spectroscopy**

1. Obtain a NMR spectrum of the product. Consult with your laboratory instructor about how to do this.

2. Assign all the NMR peaks in the spectrum.
Post-Lab Questions

1. What is Fuming Sulfuric Acid and what is its role in step 2 of the procedure?

2. AlCl₃ is a corrosive and toxic compound whose use has been avoided in our procedure. It reacts violently with Water. Give an equation for what happens when this compound is hydrolyzed in Water. What reagents would we have used if AlCl₃ had been our choice for a catalyst?

3. Why are Friedel-Crafts alkylations usually carried-out by adding the alkylating agent to the aromatic compound and not the other way around?

4. Heating any of the three isomeric dimethylbenzenes with HF in the presence of BF₃ to 80°C leads to the equilibrium mixture shown. Formulate a mechanism for these isomerizations, starting with 1,2-dimethylbenzene and simply using H⁺ to represent the acid. Why is the equilibrium concentration of the 1,2-isomer the lowest?

![Image of dimethylbenzenes with percentages: 18% 1,2-Dimethylbenzene (α-Xylene), 58% 1,3-Dimethylbenzene (m-Xylene), 24% 1,4-Dimethylbenzene (p-Xylene).]

5. Attempted alkylation of benzene with 1-chlorobutane in the presence of AlCl₃ gave not only the expected butylbenzene, but also as a major product, (1-methyl-propyl)benzene. Write a mechanism for this reaction.