Electrophilic Aromatic Substitution: Synthesis of 4-Bromoacetanilide

**Reaction**

\[
\begin{align*}
\text{Acetanilide} & \quad + \quad \text{Br}_2 & \quad \rightarrow & \quad \text{4-Bromoacetanilide} \\
\text{H}_3\text{C} & \quad - \quad \text{C} & \quad - \quad \text{N} & \quad - \quad \text{H} & \quad + & \quad \text{Br}_2 & \quad \rightarrow & \quad \text{HBr} \\
\end{align*}
\]

**Purpose:**
This mechanism is a classic example of electrophilic aromatic substitution. An amine may lead to di- and tri-substituted products. If an amide is used in place of the amine, monosubstitution usually predominates (the electron-withdrawing carbonyl group makes the benzene ring less nucleophilic). This ortho-, para-directing group will tend to only add groups para to itself because of the steric bulk of the amide group.

**Experimental Procedure.** (Estimated time: 1.5 h.). Unless otherwise noted, all manipulations should be done in the chemical fume hood.

<table>
<thead>
<tr>
<th>Physical Properties of Reactants</th>
<th>Compound</th>
<th>MW</th>
<th>Amount</th>
<th>mmol</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetanilide</td>
<td>135.17</td>
<td>25 mg</td>
<td>0.19</td>
<td>114</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glacial Acetic Acid</td>
<td>60.05</td>
<td>4 drops</td>
<td></td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bromine-acetic acid solution</td>
<td>3 drops</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Place 25 mg (0.19 mmol) of acetanilide into a 3.0-mL conical vial. Add 4 drops of glacial acetic acid using a medicine dropper. Stirring with a glass rod may be necessary to help dissolve the acetanilide. Now, in the hood, add to the clear solution three drops of the bromine-acetic acid solution (wear gloves and, of course, goggles. **Use extreme caution.** Bromine burns can be quite severe). Cap the vial immediately. Allow the reddish-brown solution to stand at room temperature for 10 min with intermittent shaking (use caution). During this period, yellow-orange colored crystals precipitate from the solution.

Add 0.5 mL of distilled water to the reaction mixture with swirling, followed by 5 drops of aqueous sodium bisulfite solution (33%). This treatment destroys the unreacted bromine (and its residual color) and results in white crystals. Cool the reaction mixture in an ice bath for 10 min to maximize the yield of product.

Collect the white crystals of 4-bromoacetanilide by vacuum filtration. Wash the filter cake with three 0.25-mL portions of cold water and partially dry by drawing air through the crystals under reduced pressure for approximately 5 min.

Weigh and calculate the percent yield. Obtain melting point and compare with literature data. Obtain the $^1$H NMR spectra and compare to what is given.
**Questions (to be answered in your notebook):**

1. Define the terms: nucleophile and electrophile.

2. Why does the sodium bisulfite make the solution colorless? i.e. what kind of a reaction is occurring?

3. Which NMR spectrum (below) is the proton and which is the carbon spectrum? How do you know?

**Spectral interpretation:**
Interpret the NMR spectra given below in your notebook. (The smaller peaks are impurities).

**Sample: p-bromoacetanilide**

**Solvent: d<sub>6</sub>-DMSO**