
**Diazonium Coupling Reaction: Methyl Red**

Common names: methyl red  
CA number: [493-52-7]  
CA name as indexed: benzoic acid, 2-[[4-(dimethylamino)phenyl]azo]-

**Purpose.** In this experiment you will learn the process of generating arenediazonium salts in solution. The arenediazonium salt generated will be used in an electrophilic aromatic substitution reaction (diazo coupling) to prepare an azobenzene derivative. Many azobenzene derivatives, including the one prepared here, have extensively conjugated \( \pi \)-electron systems. Because these are highly colored compounds, they are generally referred to as azo dyes.

**Prior Reading**

*Technique 5: Crystallization*

Use of the Hirsch Funnel (pp. 74–75)  
Craig Tube Crystallization (pp. 75–77)

**REACTION**

\[
\text{Anthranilic acid} \quad \begin{array}{c}
\downarrow \\
\text{NaNO}_2, \text{HCl, H}_2\text{O, 0°C} \\
\uparrow \\
\text{Anthranil diazonium chloride}
\end{array} \quad \begin{array}{c}
\downarrow \\
\text{Anthranil diazonium chloride} \\
\text{N,N-Dimethylaniline} \\
\end{array} \quad \begin{array}{c}
\downarrow \\
\text{Methyl red}
\end{array}
\]

**DISCUSSION**

The coupling of a diazonium salt to a suitable aromatic substrate is an example of an aromatic electrophilic substitution reaction. When primary aromatic (and also aliphatic) amines (ArNH\(_2\)) are treated with nitrous acid (NaNO\(_2\) + HCl = HONO), they are converted into diazonium cations, ArN\(_2^+\). In solution, nitrous acid (HONO) is in equilibrium with its anhydride, dinitrogen trioxide (N\(_2\)O\(_3\)), which is the actual diazoating agent. The primary amine reacts with the dinitrogen trioxide to form a nitrosamine:

\[
\text{Ar—NH}_2 + \text{N}_2\text{O}_3 \rightarrow \text{Ar—NH—N} = \ddot{\text{O}} + \text{HONO}
\]  
(a nitrosamine)
The nitrosamine is in equilibrium with its tautomer, a diazoic acid. The diazoic acid then undergoes dehydration to form the diazonium salt. Diazonium salts are explosive when dry, and therefore are generally not isolated.

\[
\text{Ar} - \hat{\text{N}} \hat{\text{H}} - \hat{\text{N}} = \hat{\text{O}}: + \text{H}_2\text{O}^+ \rightleftharpoons \text{Ar} - \hat{\text{N}} = \hat{\text{N}} - \hat{\text{O}}\text{H}^+ + \text{H}_2\text{O}^+ \\
\quad \text{(a nitrosamine)} \quad \text{(a diazoic acid)}
\]

\[
\text{Ar} - \hat{\text{N}} = \hat{\text{N}} - \text{O}^+ \text{H}^+ + \text{H}_2\text{O}^+ \rightarrow \text{Ar} - \text{N} = \text{N}: + 2 \text{H}_2\text{O}^+ \\
\quad \text{Diazonium ion}
\]

Reaction of the diazonium salt with various aromatic compounds leads to the formation of azo derivatives by what is generally called a "coupling reaction," but is mechanistically simply an ordinary electrophilic aromatic substitution reaction. The mechanism of the reaction is given here:

Azo dyes find use as acid–base indicators. For example, Methyl Red prepared in this experiment, Methyl Orange and Congo Red are well-known acid–base indicators. Azo dyes are commonly used in the textile, food and cosmetic industries; FD&C Yellow No. 6, a yellow azo dye is used to color candy, ice cream, beverages, and so on. Several azo dyes (including Butter Yellow and FD&C Red No. 2) have been banned by the FDA from use in foods, drugs, and cosmetics in the United States because of suspected carcinogenic properties.
**EXPERIMENTAL PROCEDURE**

Estimated time for the completion of the experiment: 3.0 h.

The reaction is shown on p. 319.

<table>
<thead>
<tr>
<th>Compound</th>
<th>MW</th>
<th>Amount</th>
<th>mmol</th>
<th>mp (°C)</th>
<th>bp (°C)</th>
<th>d</th>
<th>nD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthranilic acid</td>
<td>137.14</td>
<td>65 mg</td>
<td>0.47</td>
<td>146–147</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concd HCl</td>
<td></td>
<td>150 μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td></td>
<td>800 μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium nitrite</td>
<td>69.0</td>
<td>36 mg</td>
<td>0.52</td>
<td>271</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N,N-Dimethylaniline</td>
<td>121.18</td>
<td>89 μL</td>
<td>0.71</td>
<td>194</td>
<td>0.96</td>
<td>1.5582</td>
<td></td>
</tr>
<tr>
<td>Sodium acetate</td>
<td>82.03</td>
<td>68 mg</td>
<td>0.83</td>
<td>324</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10% aq. NaOH</td>
<td></td>
<td>100 μL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CAUTION:** When dry, benzenediazonium 2-carboxylate detonates violently upon being scraped or heated. It must, therefore, be kept in solution at all times.

**Reagents and Equipment.** Equip a 3.0-mL conical vial with a magnetic spin vane and an air condenser. Weigh and add 65 mg (0.48 mmol) of anthranilic acid to the vial. Now add a solution of 150 μL of concentrated hydrochloric acid dissolved in 400 μL of water to the vial, using a Pasteur pipet.

**CAUTION:** When preparing the acid solution, the acid must be added to the water. Dispense these reagents using automatic delivery pipets.

If necessary, warm the mixture, with stirring, on a hot plate magnetic stirrer to obtain a homogeneous solution. Cool the solution in an ice bath, with stirring, for 10 min.

In a 10 × 75-mm test tube, or a small vial, prepare a solution of 36 mg (0.52 mmol) of sodium nitrite dissolved in 200 μL of water. Cool this solution in an ice bath.

**Reaction Conditions.** When both solutions in the ice bath are cooled to a temperature below 5 °C, slowly add (dropwise) the nitrite solution to the stirred anthranilic acid solution, while maintaining the temperature below 5 °C. This transfer is accomplished using a Pasteur pipet. The solution must be kept cool so that the diazonium salt will not hydrolyze to the corresponding phenol.
After a period of 4–5 min, check the clear solution of anthranil diazonium chloride for the presence of excess nitrous acid by placing a drop of the solution on a piece of potassium iodide–starch test paper. If an excess is present, the test paper gives an immediate blue color. If no color is obtained, prepare additional nitrite solution and add as before until a positive test is observed.

Remove the air condenser from the reaction vial containing the solution of anthranil diazonium chloride. Fairly rapidly, add 89 μL (85 mg, 0.71 mmol) of N,N-dimethylaniline (automatic delivery pipet). Reattach the air condenser.

**CAUTION:** This aniline derivative is toxic and should be dispensed in the hood.

Stir the solution for an additional 15 min, keeping the temperature below 5 °C. Prepare a solution of 68 mg (0.83 mmol) of sodium acetate dissolved in 200 μL of water in a 10 × 75-mm test tube. Transfer this solution (Pasteur pipet) to the reaction mixture. Make this addition without removing the air condenser. Maintain the resulting solution at 5 °C, with stirring, for an additional 20 min. Remove the reaction vial from the ice bath and allow it to stand for 15 min in order to warm to ambient temperature.

Now add 100 μL of 10% aqueous NaOH solution (automatic delivery pipet) to the solution. Allow the reaction mixture to stand at room temperature for about 30 min. The formation of the azo compound is a very slow reaction, but the rate of formation is increased by raising the pH of the solution.

**Isolation of Product.** Collect the precipitate of crude Methyl Red dye by vacuum filtration using a Hirsch funnel ( ). Rinse the reaction flask with 0.5 mL of water and use this rinse to wash the crystals. Then wash the crystals with 0.5 mL of 3 M acetic acid, to remove unreacted N,N-dimethylaniline from the product, followed by another wash with 0.5 mL of water. This last wash is usually pale pink in color.

**NOTE.** Dispense the small amounts of water and acetic acid using a calibrated Pasteur pipet.

**Purification and Characterization.** Dissolve the crude product in 500 μL of methanol. If necessary, warm the mixture in a beaker of hot water to aid in the dissolution. Cool the solution in an ice bath and collect the resulting crystals of Methyl Red by vacuum filtration using a Hirsch funnel. Dry the material on filter paper or under vacuum at room temperature.

Weigh the product and calculate the percent yield. Determine the melting point and compare it to the value given in the literature. If further purification is desired, recrystallize the material from toluene using a Craig tube.

**QUESTIONS**

6-168. In the experiment, a point is made that the formation of the azo compound is a slow reaction, but that the rate is increased by raising the pH of the solution. Why is this necessary? In other words, how does the pH of the solution affect the reactivity of the N,N-dimethylaniline reagent?

6-169. In relation to Question 6–168, diazonium salts couple with phenols in slightly alkaline solution. What effect does the pH of the solution have on the reactivity of the phenol?

6-170. Starting with the appropriate aromatic amine and using any other organic or inorganic reagent, outline a synthetic sequence for the preparation of the following azo dyes:

(a)  
\[
\text{CH}_2\text{NH}_2\cdot\text{HCl}
\]

Chrysoidine
6-171. What is the main structural feature of the azo dyes that causes them to be colored compounds?

6-172. Methyl Orange is an acid-base indicator. In dilute solution at pH > 4.4, it is yellow.

At pH = 3.2 the solution appears red. Draw a structure of the species that is formed at the lower pH if the acid proton adds to the azo nitrogen atom adjacent to the aromatic ring containing the $\text{SO}_3^-$ group. Why does the proton add to this particular nitrogen when two other nitrogen atoms are available in the molecule?

For reviews on diazo compounds and azo dyes see:


Selected coupling reactions with diazonium salts from Organic Syntheses:


The synthesis of Methyl Red is also given in Organic Syntheses:


The present experiment is an adaptation of that given in