Experiment 14: Multi-step synthesis of Benzocaine

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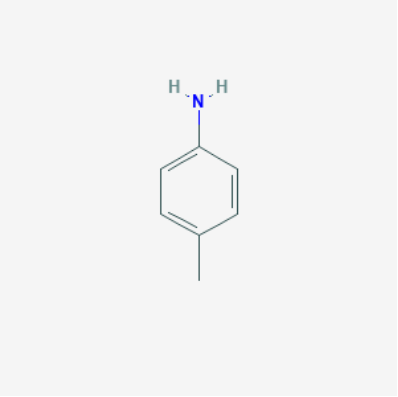
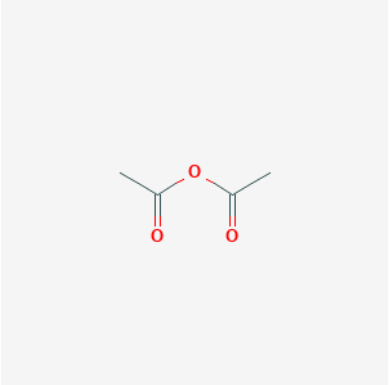
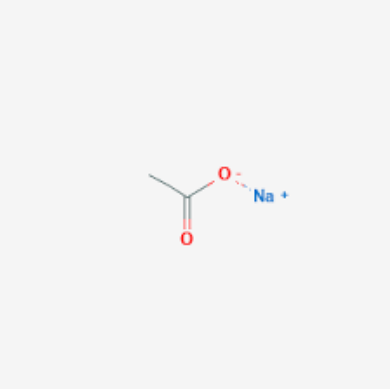
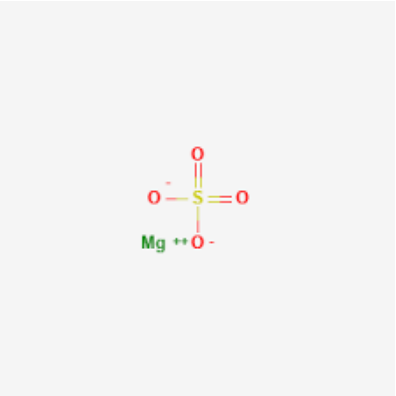
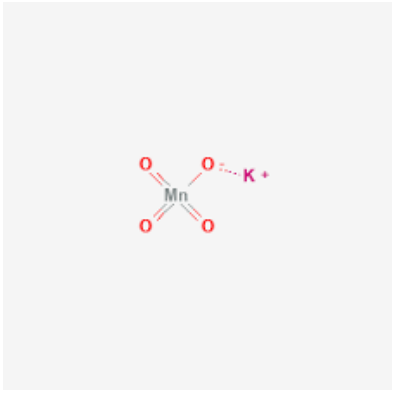
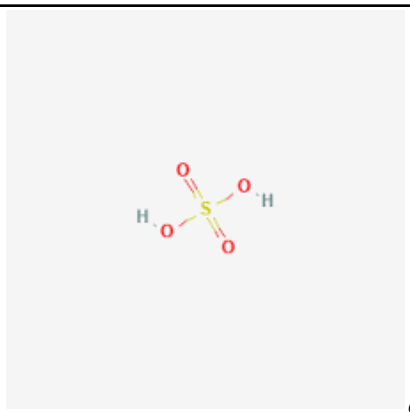
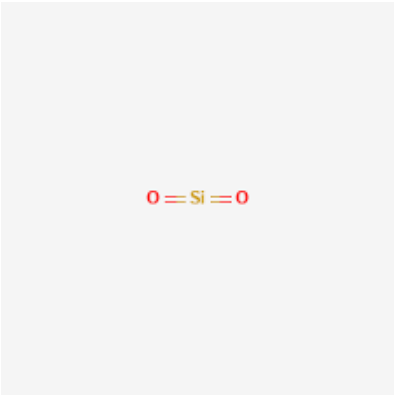
Introduction:

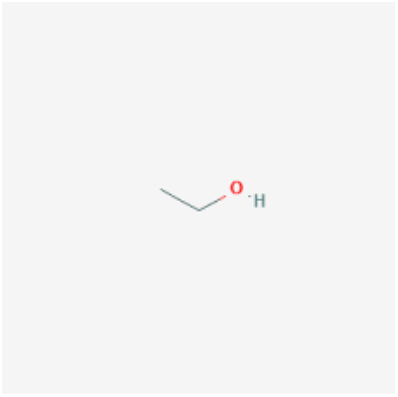
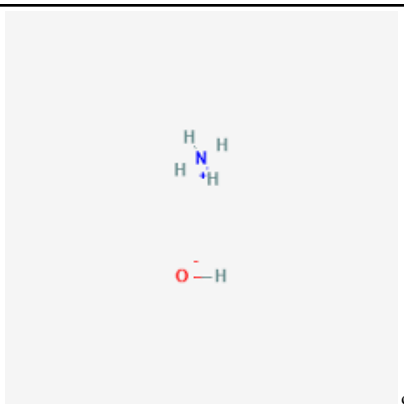
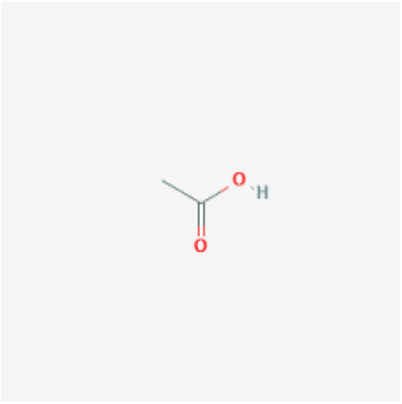
For this lab the preparation of benzocaine through a multistep organic synthesis, it was broken down into 4 different parts. First part N-Acetyl-p-Touidine (Protection) is then synthesized into N-acetyl-p-toluidine. Second part was the synthesis of p-Acetamidobenzoic Acid (Oxidation). N-acetyl-p-toluidine was then synthesized into p-Acetamindobenzoic Acid. Third part was the synthesis of p-Aminobenzoic Acid (Deprotection). P-Acetamindobenzoic Acid was then synthesized into p-Aminobenzoic Acid. The last part, part four was the Synthesis of Ethyl p-Aminobenzoate (Benzocaine) (Esterfication). This took p-Aminobenzoic Acid into ethyl p-aminobenzoate. This last part was the end of this multi-step synthesis. The IR was taken and will be used to compare that to theoretical IR of each part of the synthesis.

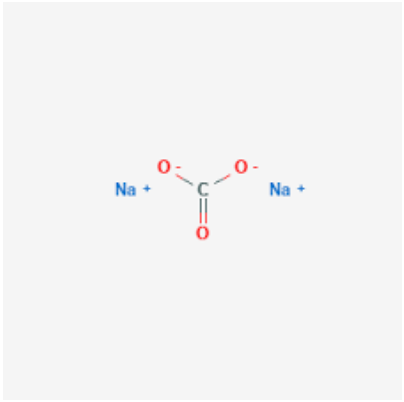
Table 1: Physical Properties Table:

Compound Structure	Name	Molar Mass (g/mol)	Physical Structure
 [1]	p-toluidine	107.15	Hard brown granulated
H - Cl	Hydrochloric Acid	36.46	Clear Liquid

 2	Acetic Anhydride	102.09	Clear Liquid
 3	Sodium Acetate	82.03	Clear Liquid
 4	Magnesium Sulfate	120.37	White Powder

 5	Potassium permanganate	158.03	Black/purple granulated
 6	Sulfuric Acid	98.08	Cloudy liquid
 7	Celite	74.08	White Powder

 8	Ethanol	46.07	Clear Liquid
 9	Ammonium Hydroxide	35.04	Clear Liquid
 10	Glacial Acetic Acid	60.05	Clear Liquid

 11	Sodium Carbonate	105.99	Cloudy liquid

Structure/Reaction Scheme:

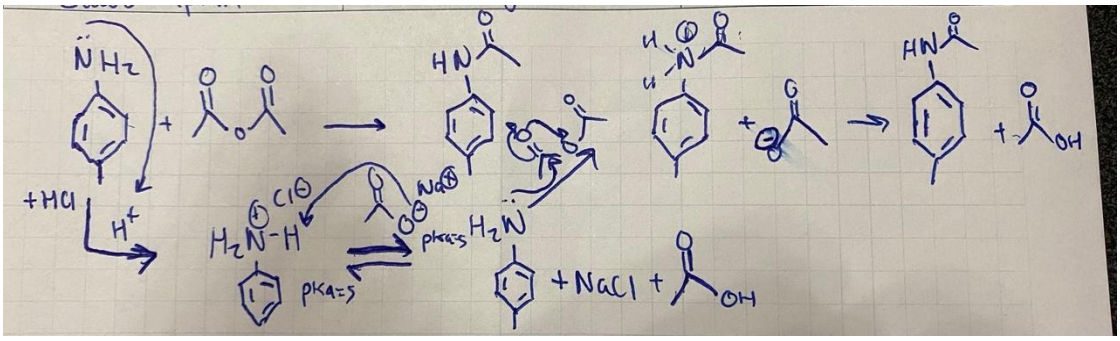


Figure 1: Week 1 Reaction scheme of N-Acetyl-p-Touidine (Protection)

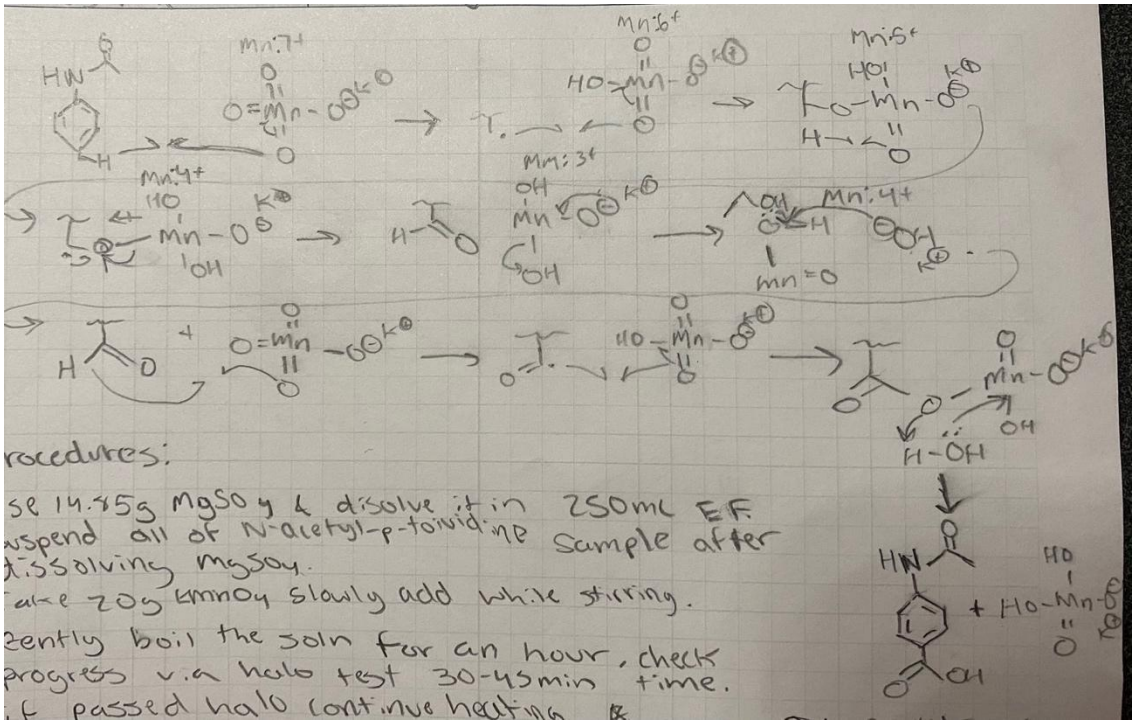


Figure 2: Week 2 Reaction Scheme Synthesis f p-Acetamidobenzoic Acid (Oxidation)

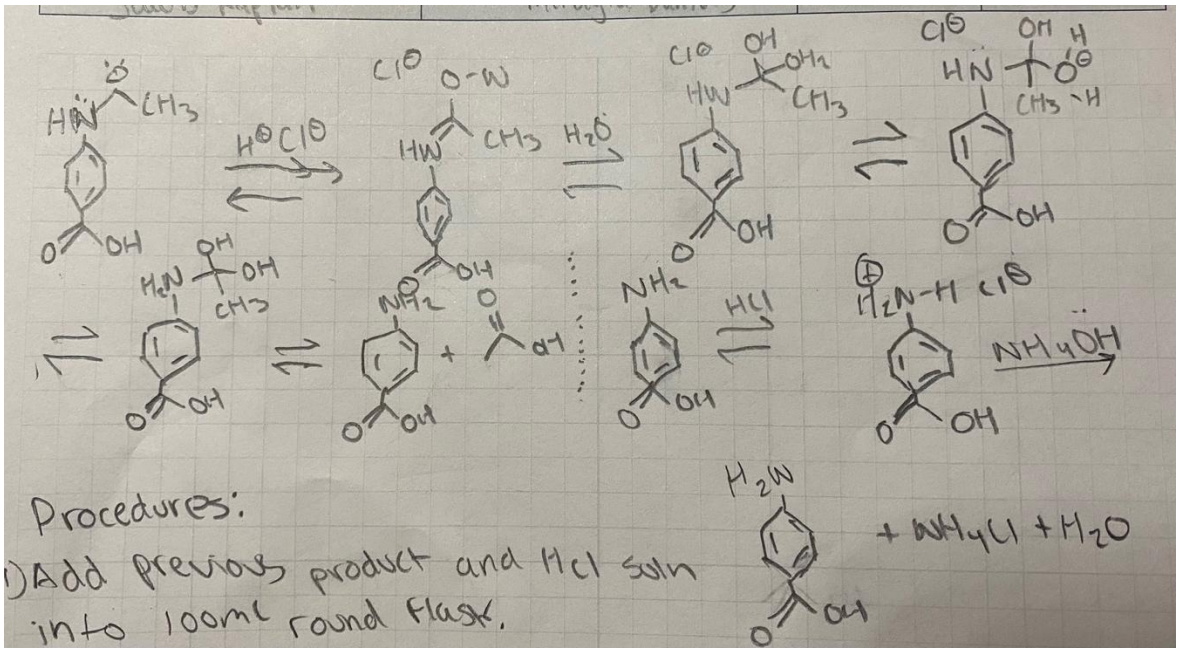


Figure 3: Week 3 Reaction Scheme Synthesis of p-Aminobenzoic Acid (Deprotection)

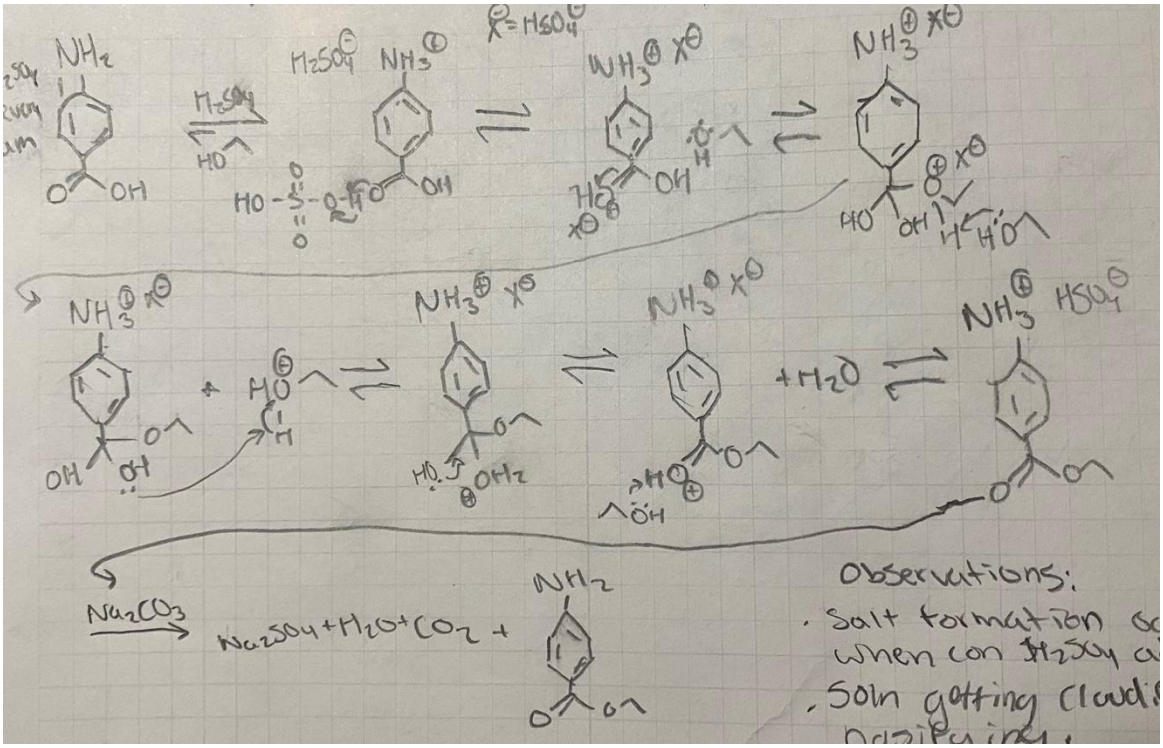


Figure 4: Week 4 Reaction Scheme Synthesis of Ethyl p-Aminobenzoate (Benzocaine) (Esterfication)

Procedure:

Week 1: Reaction of N-Acetyl-p-Touidine (Protection)

Place 5.33g of p-toluidine in a 250 mL E. flask and dissolve with 133 mL of water with 5 mL of concentrated HCL. Warm the solution to 50°C. After, add 5.6 mL of acetic anhydride and stir rapidly. Immediately add 18.6 mL of sodium acetate buffer and stir for 10 minutes. After mixing cool solution in an ice bath to allow crystallization. Filter the crystals with a vacuum filter and wash the product 3 times with cold water. Let dry, and weigh and take the boiling point of the product.

Week 2: Synthesis f p-Acetamidobenzoic Acid (Oxidation)

Dissolve 14.85 g of MgSO4 In 250 mL of water in an E flask. Suspend product from the previous reaction into the reaction solution. Add 20 g of KMnO4 slowly into the mixture while

stirring. Gently boil the solution for 1 hour on a hot plate. Check the progress of the synthesis via the halo test. Once the halo test passed filter warm reaction through 20 g celite and 200 mL water filter bed. Recover the product and acidify the solution with H_2SO_4 till a pH of 2-3. Collect the sample precipitant via vacuum filtration. Let dry, and weigh, take the boiling point, and IR of the product.

Week 3: Synthesis of p-Aminobenzoic Acid (Deprotection)

Add the previous reaction product to a 32 mL HCl solution in a 100 mL round flask. Place the flask in a heating mantel apparatus to undergo reflux. After 30 minutes of reflux, cool the solution and transfer it into a 250 mL E flask and add 10 mL of water in. Slowly add 65 mL of NH_4OH to the solution to basify the solution. Add 1 mL of glacial acetic acid to the solution and cool in an ice bath. Collect the product using vacuum and let dry, and weigh and take the boiling point of the product.

Week 4: Synthesis of Ethyl p-Aminobenzoate (Benzocaine) (Esterification)

Dissolve the previous week's product into 30 mL of 95% ethanol in a 250 mL round bottom flask. Add 1 mL of concentrated H_2SO_4 before reflux. Place the flask in a heating mantel apparatus to undergo reflux. After refluxing for 90 min take the solution out to cool to room temperature. Transfer to 400 mL beaker and add around 60 mL 10% Sodium Carbonate solution slowly until pH is 9 or higher. Pour the solution into a separatory funnel and extract the basic aqueous solution with two 50 mL portions of diethyl ether. Combine ether extracts in an E flask and dry the solution over anhydrous $MgSO_4$. Using a rotavapor apparatus reduce the volume of the solution until the pure product is left. Weigh and IR the product.

Observations/Results:

Week 1: Reaction of N-Acetyl-p-Touidine (Protection)

Observations: when p-toiuline was added the solution turned yellow and clear. It took a while to dissolve under heat. Once sodium acetate was added the solution turned cloudy white and precipitate started to form.

Results: % Yield: .0418 mol/ .049 mol x 100 = 85% MP: 143°C

Week 2: Synthesis f p-Acetamidobenzoic Acid (Oxidation)

Observations: The solution turned purple immediately after adding KMnO4. After 1 hour the solution turned brown and slurry. Halo test when negative had a purple ring around the brown slur. When the halo test passed no purple halo showed around the product. The product after celite filtration was a clear liquid. Cloudy precipitates formed after adding H2SO4.

Results: % yield: .021/ .0418 x 100 = 50.7%

Week 3: Synthesis of p-Aminobenzoic Acid (Deprotection)

Observations:

Results: % Yield: .007 mol/ .021 mol x 100 = 33% MP: 183°C

Week 4: Synthesis of Ethyl p-Aminobenzoate (Benzocaine) (Esterification)

Observations: Salt formation in the form of a precipitant form when concentrated H2SO4 is added. The solution was getting cloudier as it was basifying.

Results: % yield: .0204 mol / .007 mol x 100 = 291%

Conclusion:

For this multi-week synthesis project at the end of each lab, there were several steps to record proper results. The first was to measure the weight and get the percent yield. Next, we record the melting point of the sample and compare it to the theoretical melting point. Lastly, we take the

sample and run and IR and NMR on it. This gets us the chemical similarities between different functional groups and the chemical structure in the molecule.

For stock p-toluidine, the sample has 3 different functional groups NH2, benzene ring and, CH3. The IR shows 3300-3000 spikes for amines, 1600-1585 for the aromatic group, and 1390-1365 for the methyl group. On the NMR p-toluidine shows a very large spike at 2.2 for the methyl group, a spike at 3.5 for the amine group, a double at 6.6 and 6.9 for H bonded groups.

Week 1 product was N-acetyl-p-toluidine, their IR showed peaks in the region of 1450-1600 for the aromatic group and larger spikes towards 1660 for the amide group. Also shown is the C-H stretch between alkene 2900-2965, and 3070-3120 for aromatic C-H stretch groups. The last peak showed at 3280 for the N-H stretch. NMR showed NH broad peak at 1.1, a double peak at 2.1 for the methyl group. Also, 7.3 doublet for the aromatic ring.

Week 2 product p-acetamidobenzoic acid shows very similar peaks for the IR to that of the previous weeks' results besides it shows large O-H stretching peaks due to the carboxylic acid group at 2800. Also shown, was a 3300 peak for the N-H stretch. NMR shows the same peaks for the methyl group. Aromatic groups are shown as two doublets towards 7.6-7.8. Also, a spike around 10.3 for the shifted O=C-OH bond.

Week 3 the product p-aminobenzoic acid shows few distinct peaks for the IR at 1600 was the carboxylic acid group, and 1665 was the amide group. Same C-H and N-H stretch peaks, but with a new O-H stretch peak for carboxylic acid at 3450. NMR shows us small doublet peaks at 6.9 for the amino groups and 7.8 most likely for the aromatic ring.

Week 4 the product ethyl p-aminobenzoate had an N-H bend at 1590. C=O ester stretch was 1670. The other groups have peaked around 2815-2830 for the C-H alkene stretch and from 3300-3400 was for the primary amine. On the NMR it shows a large triplet spike at 1.6-1.7 for

double-bonded oxygen. Also shown is the broad peak around 3.5 for the NH2 group. A quartet formed at 4.3 for the methyl and ester group on the molecule. As normal, the doublet at 6.7 was for the aromatic group.

References:

[1] "p-Toluidine." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/p-Toluidine.

[2] "Acetic Anhydride." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Acetic-anhydride.

[3] "Sodium Acetate." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Sodium-acetate.

[4] "Magnesium Sulfate." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Magnesium-sulfate.

[5] "Potassium Permanganate." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Potassium-permanganate.

[6] "Sulfuric Acid." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Sulfuric-acid.

[7] "SID 134987421 - PubChem." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/substance/134987421.

[8] "Ethanol." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/ethanol.

[9] "Ammonium Hydroxide." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Ammonium-hydroxide.
[10] "Acetic Acid." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Acetic-acid.
[11] "Sodium Carbonate." *National Center for Biotechnology Information. PubChem Compound Database*, U.S. National Library of Medicine, pubchem.ncbi.nlm.nih.gov/compound/Sodium-carbonate.