Honors Cup Synthetic Proposal

Section: **220**
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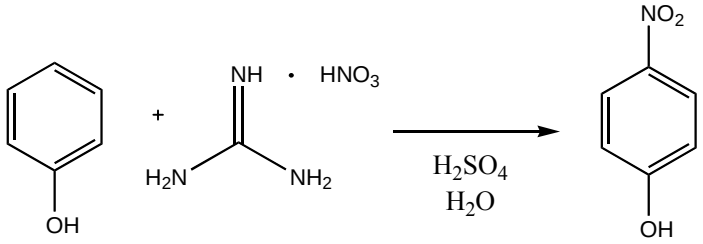
Title: Synthesis of *N*-acetyl-4-aminophenol from Phenol in Three Steps

Introduction: Acetaminophen (*N*-acetyl-4-aminophenol), sold as the brand name Tylenol, is a pain reliever and fever reducer. Unlike aspirin, ibuprofen, and other similar drugs, acetaminophen does not irritate the lining of the stomach, nor does acetaminophen cause addiction, like morphine, which makes acetaminophen an effective medicine. Acetaminophen can be synthesized in three fairly environmentally safe steps: nitration, reduction, and acetylation.

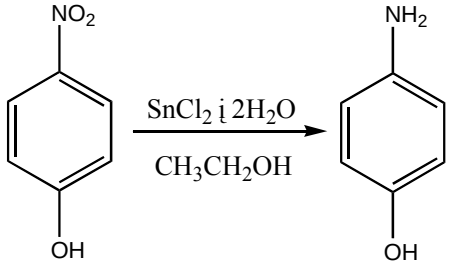
Overall synthetic reaction scheme:
Step 1:



1 *5* **2**

Nitration of phenol (**1**) into 4-nitrophenol (**2**) using guanidinium nitrate (*5*).

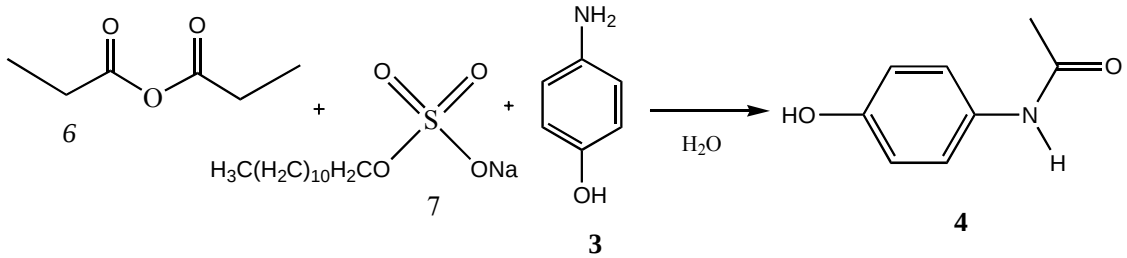
Step 2:



2 **3**

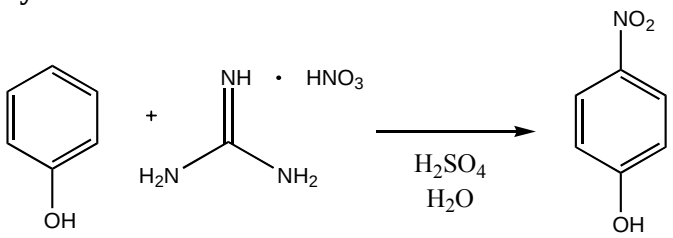
Reduction of 4-nitrophenol (**2**) into 4-aminophenol (**3**) using tin (II) chloride dihydrate in a solution of ethanol.

Step 3:



Acetylation of 4-nitrophenol (**3**) using propionic anhydride (*6*) and sodium dodecyl sulfate (SDS) (*7*) in water.

Step 1
Synthetic transformation 1:



1 *5* **2**

Nitration of phenol (**1**) into 4-nitrophenol (**2**) using guanidinium nitrate (*5*).

Experimental 1

Guanidinium nitrate (*5*) (1.318 g, 10.80 mmol) was slowly added to a well-stirred mixture of phenol (**1**) (1.016) g, 10.80 mmol) and sulfuric acid (16.20 mL, 85%), maintaining a temperature of 0-5° C. When the addition was complete, the mixture was stirred for an additional 2 h at the same temperature. The reaction mixture was then poured into ice water (~100mL). The solid obtained was filtered, washed thoroughly with water, and dried. If solid was not obtained the aqueous layer was extracted with $CHCl_3$ (4 × ~50mL). The $CHCl_3$ layers were combined and washed with 10% Na_2CO_3 (2 × ~25mL), water (2 × ~25mL) and then dried with anhydrous Na_2SO_4. After evaporation of the solvent, a brownish residue was obtained, which was purified by column chromatography to produce 4-nitrophenol. 4-nitrophenol (**2**) was identified and characterized using IR and NMR and comparison to literature data.
*A scale of 1.08:1 of project : literature for amounts of reagents was used to fit the project scale.

Expected yield: 68 % 1.0215 g

Safety, disposal and green issues 1:

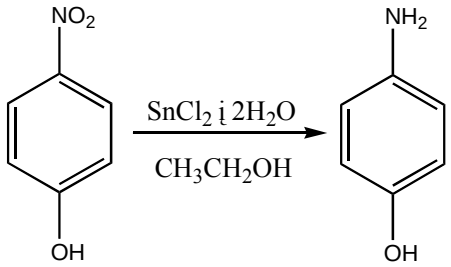
Phenol is corrosive and toxic by inhalation, skin contact, or if swallowed. There are possible risks of irreversible effects. Phenol is a possible mutagen, carcinogen, teratogen, and reproductive hazard. Care must be taken when handling phenol. There is danger of serious damage to health by prolonged exposure. As phenol readily penetrates skin, appropriate protective clothing (gloves and goggles) must be worn and phenol must be kept under the hood. MSDS recommends use of respirator. Phenol may cause serous damage to health by prolonged exposure. Avoid contact with skin and eyes, and wash areas that come into contact with phenol. Polyethylene glycol solution is recommended for washing off splashes. Splashes are much more serious when phenol is mixed with chloroform. Wearing an apron is recommended.

Guanidinium nitrate is harmful if swallowed and irritating to eyes, respiratory system, and skin. Guanidinium nitrate is a strong oxidizing agent and should be kept away from combustibles and flames. Wear appropriate protective clothing. Sulfuric acid is highly corrosive. Never add water to sulfuric acid.

These materials do not pose serious environmental hazards according to the Sigma-Aldrich website and MSDS but should still be disposed of properly. Appropriate gloves, goggles and protective clothing should always be worn, and chemicals should be handled in the hood and be capped when not in use.

Step 2

Synthetic transformation 2:



2 **3**

Reduction of 4-nitrophenol (**2**) into 4-aminophenol (**3**) using tin (II) chloride dihydrate in a solution of ethanol

Experimental 2

A mixture of 1,4-nitrophenol (0.801g, 7.34 mmol), tin (II) chloride dihydrate (8.279 g, 36.7 mmol) in 15 mL HPLC grade ethanol was heated at 70°C under nitrogen. After the 30 minutes the starting material has disappeared and solution was allowed to cool down and then poured into ice. The pH was made slightly basic (pH 7-8) by addition of 5% aqueous sodium bicarbonate before being extracted with ethyl acetate. The organic phase was washed with brine and treated with charcoal, then dried with sodium sulfate. Impurities can be separated through column chromatography. Evaporation of the solvent using the rotovap leaves 4-aminophenol. The purity and identity of product can be verified through TLC and NMR and IR spectroscopy. (Although the literature uses absolute ethanol, charcoal filtered anhydrous ethanol was substituted due to the prohibitive cost of absolute ethanol).
*The amounts of reactants used were changed to fit the scale of the project in a 0.734:1 ratio.

Expected yield: 91% 0.729 g

Safety, disposal and green issues 2:

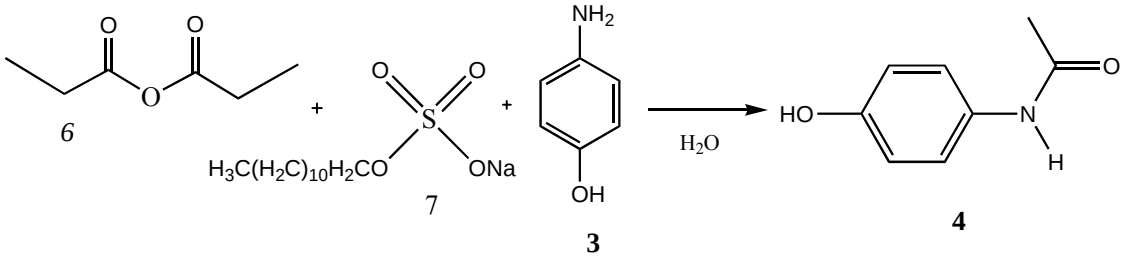
Tin (II) chloride dihydrate is corrosive, harmful if swallowed, and causes burns. In case of into contact with skin, wash with copious amounts of water. This material does not pose a serious environmental hazard, but should still be disposed of properly.

4-nitrophenol is toxic by inhalation, skin contact, or ingestion with possible cumulative effects and is a mutagen. A respirator is recommended by MSDS. As 4-nitrophenol readily penetrates skin, proper gloves should be worn. Polyethylene glycol is recommended in case of splashes. 4-nitrophenol is photosensitive. This material is harmful to aquatic organisms so remaining reactant after step 2 should be disposed of accordingly.

Chemicals should be handled under the hood and should be capped when not in use. Appropriate protection: gloves, goggles, apron should be worn.

Step 3

Synthetic transformation 3:



Acetylation of 4-nitrophenol (**3**) using propionic anhydride (*6*) and sodium dodecyl sulfate (SDS) (*7*) in water.

Experimental 3

Sodium dodecyl sulfate (26.73 mg, 9.27 x 10^{-2} mmol) was added to a stirred heterogeneous suspension of 1,4-aminophenol (0. 73 g, 6.68 mmol) in water (26.7 mL) until a homogeneous solution was formed. If turbidity persisted, the mixture was warmed to obtain a clear solution. Propionic anhydride (1.30 g, 10.02 mmol) was added to the mixture over a period of 5 minutes. The acetylated product precipitated within 5-10 minutes. The precipitated product was filtered and washed with water. The product was dried by spreading it out on a watch glass/filter paper between lab days. If the product did not precipitate, the reaction mixture was extracted with ethyl acetate (2 x ~25 mL). The combined organic extracts were dried with anhydrous sodium sulfate and the solvent was removed in a rotary evaporator under reduced pressure yielding the pure product which can be identified by NMR or IR spectroscopy. (If separation of impurities is needed, column chromatography can be used).
(Amounts of reagents used were scaled to produce 1 gram of final product.)

* Note: Calculations were done, accounting for percent yields, to produce 1g final product
Expected yield: 99 % 1 g

Safety, disposal and green issues 3:

Propionic anhydride is corrosive, combustible, and causes burns. Place in closed containers for disposal. Sodium dodecyl sulfate is irritating to the skin, eyes, and respiratory system. Sodium dodecyl sulfate is hygroscopic and should be capped whenever possible.

The above two materials do not pose environmental hazards according to the Sigma-Aldrich website and MSDS but should still be disposed of properly.

4-aminophenol (produced by step 2) is toxic by ingestion, inhalation, or skin contact. Chemical is a possible mutagen, teratogen, and reproductive hazard. Proper protective clothing should be worn, and chemical should be handled under hood. MSDS recommends respirator. 4-aminophenol is photosensitive. 4-aminophenol is very toxic to aquatic ecosystems with possible long term effects, and any remaining 4-aminophenol should be disposed of appropriately. Acetaminophen is harmful if swallowed and irritating to the eyes and respiratory system, but is not considered a serious environmental hazard.

Gloves and goggles should be worn. Chemicals should be capped and used under hood.

Overall budget:

Chemical	Supplier	Cost	Amt. Needed	Total
Phenol	Sigma-Aldrich	$0.16/gram	1.02 g	$0.16
Guanidinium Nitrate	Aldrich	$0.18/gram	1.32 g	$0.24
Sulfuric Acid	Aldrich	$0.05/gram	29.8 g	$1.49
Tin (II) Chloride Dihydrate	Aldrich	$0.30/gram	8.28 g	$2.48
Sodium Dodecyl Sulfate (SDS)	Aldrich	$0.93/gram	0.027 g	$0.03
Propionic Anhydride	Aldrich	$0.41/gram	1.30 g	$0.53
Sodium Carbonate	Aldrich	$0.08/gram	~8 g	$0.24
Sodium Sulfate	Aldrich	$0.11/gram	~10 g	$1.04
Charcoal	Aldrich	$0.12/gram	~10 g	$1.17

Total costs per synthesis: $7.38

Other chemicals used (seen in class): ethanol, chloroform, water, ice, brine, sodium bicarbonate, ethyl acetate, for TLC and column chromatography: hexanes, ethyl acetate, silica, etc.

References (include at least two different sources for your experimentals):

Step 1:

Kamal, A.; Kumar, B. A.; Arifuddin, M.; Patrick, M. *Ultrasonics Sonochemistry.* **2004**, *11*, 455-457. **

Ramana, M. M. V.; Malik, S. S.; Parihar, J. A. *Tetrahedron Lett.* **2004**, *45*, 8681-8683.

Step 2:

Bellamy, F. D.; Ou, K. *Tetrahedron Lett*. **1984**, *25*, 839-42. **

Nose, A.; Kudo, T. *Chem. Pharm. Bull*. **1981**, *29*, 1159-61.

Step 3:

Bose, A. K.; Manhas, M. S.; Pednekar, S.; Ganguly, S. N.; Dang, H.; He, W.; Mandadi, A. *Tetrahedron Lett.* **2005,** *46*, 1901-1903. **

Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004,** *2004*, 1254-1260.

**The procedures for these reactions used complicated laboratory techniques beyond the scope of Chem 215/216 and unavailable technology (step 1), produced and used extremely hazardous materials (step 2), or did not detail the procedure well enough for the required purposes (step 3).