

Honors Cup Synthetic Proposal (230 V- Tu PM- W08)

Section: 230

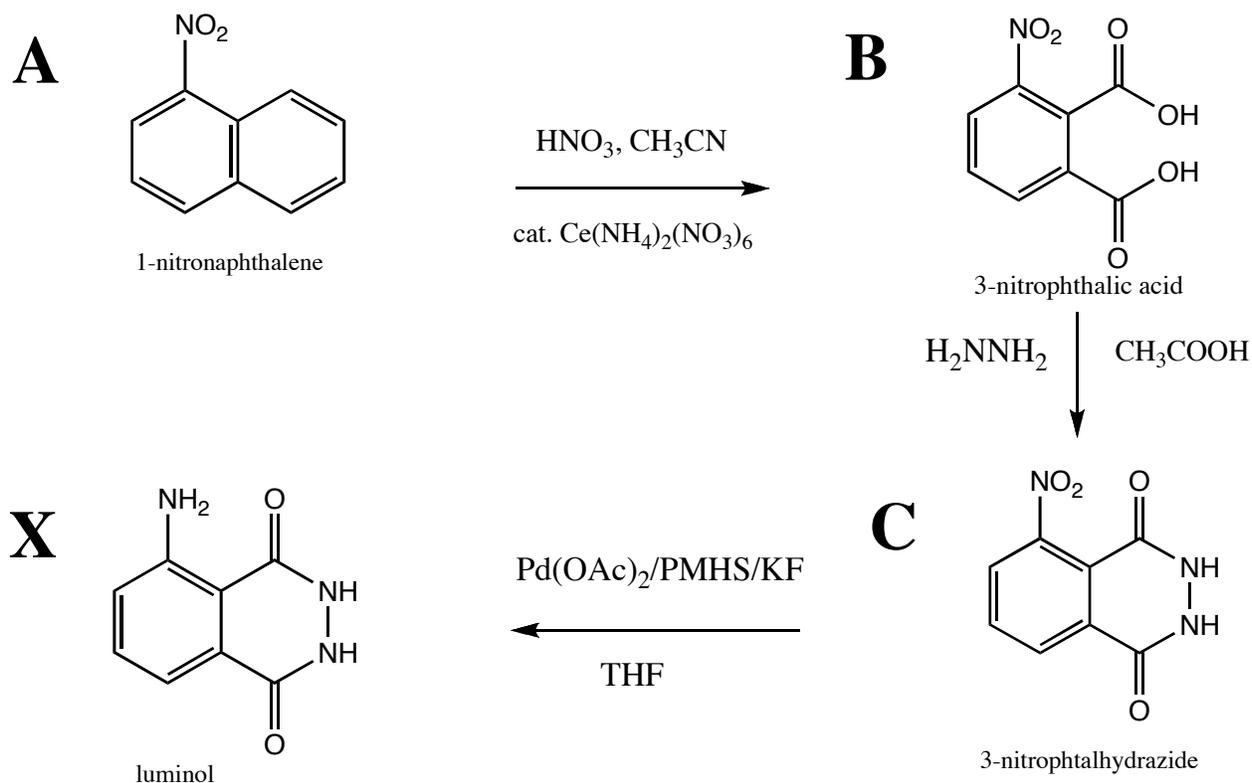
Group Members: Christina Suh, Mark Pressprich, Michelle Robinette

Title: Synthesis of luminol (5-amino-2,3-dihydro-1,4-phthalazinedione) from 1-nitronaphthalene

Introduction:

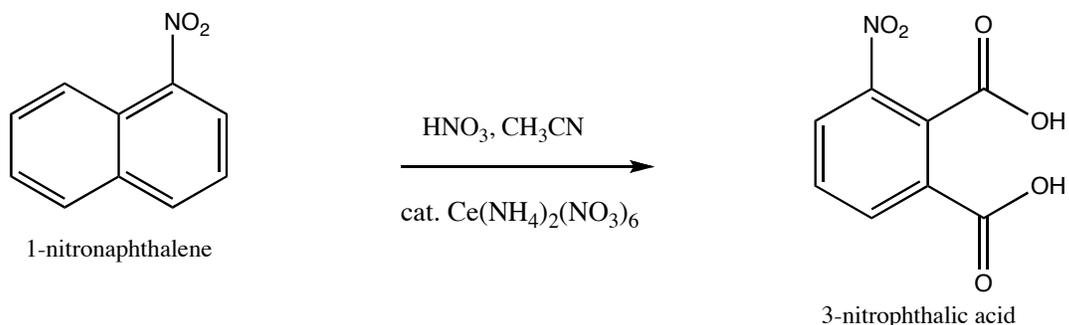
Marked by the bright blue light it emits when oxidized, luminol is one of the most well-known and widely-used chemiluminescent substances. While luminol is often used by biologists to confirm trace compounds, perhaps its most commonly recognized use is in the field of police work. The necessity of a catalyst in the oxidation of luminol by hydrogen peroxide allows forensic investigators to take advantage of luminol's chemiluminescence in the search for blood at crime scenes. In this case, the iron from the hemoglobin in blood catalyzes the oxidation, providing a quick visual "verification" of trace amounts of blood. However, this information can sometimes be misleading, as other naturally occurring compounds can also operate as catalysts.

Overall synthetic reaction scheme:



Step 1:

Synthetic transformation 1:



Experimental 1:

The first step of the synthesis was the solid-phase oxidation of 1-nitronaphthalene to 3-nitrophthalic acid in an acidic-aqueous solution employing ammonium ceric nitrate as the catalyst. 1-nitronaphthalene (3.00 g, 17.3 mmol) was dissolved in acetonitrile (5 mL) and mixed well with dilute nitric acid (69.2 mmol) in a 50 mL round-bottom flask. To this, 2.25 g ammonium ceric nitrate was added. The mixture was heated under reflux for 1 hour at 90-100° C. After being cooled to room temperature, the reaction was filtered, and the filtrate neutralized with Na_2CO_3 and washed with ethyl acetate, then adjusted to a pH of 2.0 with HCl prior to extraction of the product with methanol. 3-nitrophthalic acid was then isolated from methanol by evaporation under reduced pressure. Experimental ratios were changed to optimal levels based on data for the catalyst of interest in the reported synthesis, 5% $\text{CeO}_2/\text{Al}_2\text{O}_3$. Reflux was added to the procedure due to the low boiling point of acetonitrile (80° C).

Expected yield: 34.2% 1.25 g

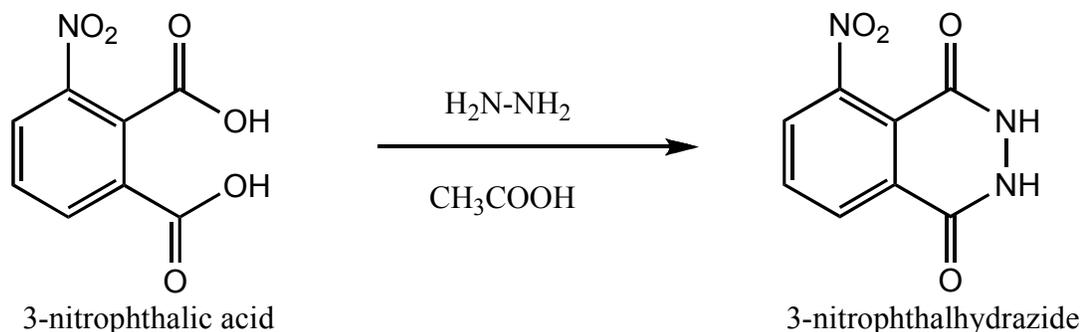
Safety, Disposal and Green issues 1:

- 1-nitrophthalic acid is a strong reducing agent which can be dangerous when mixed with nitric acid.
- Acetonitrile is highly flammable. It is toxic via skin contact, inhalation, and ingestion. As an irritant, acetonitrile may cause serious damage to the eyes. All reactions should take place under closed hoods, and safety glasses should be worn at all times.
- Nitric acid is extremely toxic and corrosive. Contact with skin or eyes can cause serious burns and permanent damage.
- Ammonium ceric nitrate is a strong oxidant that may cause fire when in contact with combustible material. It is a skin, eye, and respiratory irritant.
- For 3-nitrophthalic acid, see Safety, Disposal and Green Issues 2.

The nitric acid can be disposed in acid waste. Acetonitrile should be disposed of as an ignitable waste, as the flash point is 2° C. 1-nitrophthalic acid should be disposed of as a reducing agent, and ammonium ceric nitrate as an oxidizing agent.

Step 2:

Synthetic transformation 2:



Experimental 2: (Modernized from 1934 procedure; no open flames, no salts, no oil-bath)

In a 25 mL round-bottom flask, hydrazine (0.0055 mol or 0.176 g) and acetic acid (0.011 mol or 0.661 mL) were dissolved in 5 mL of heated H₂O. The solution was then added to 3-nitrophthalic acid (0.0055 mol or 1.16 g) in a 75 mL porcelain evaporating dish and evaporated on a hot plate. The remaining solid was put in a 25 mL beaker and heated in sand for an hour with the temperature maintained at 160° C. The solid was stirred to avoid caking. The product, 3-nitrophthalhydrazide, was then cooled to room temperature.

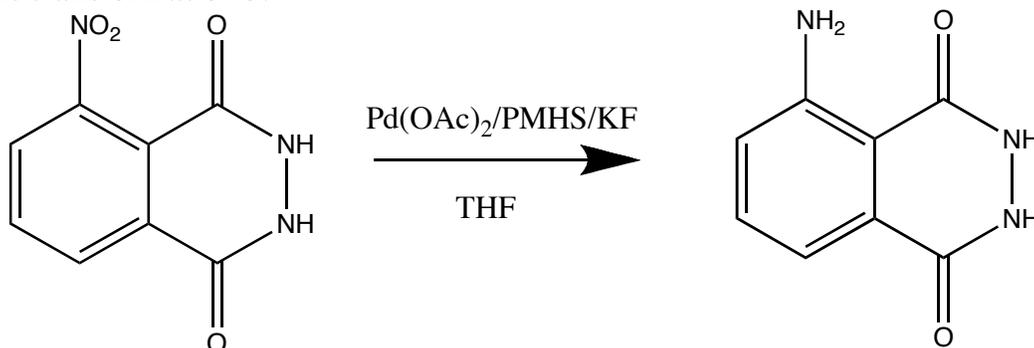
Expected yield: 99.5% 1.05g

Safety, Disposal and Green Issues:

- a) 3-nitrophthalic acid is an irritant. It is harmful if inhaled, ingested, or absorbed through the skin. Safety glasses and adequate ventilation should be used.
- b) Hydrazine may be an explosion hazard, especially when heated. It is a poison and likely a human carcinogen. It is harmful if inhaled or swallowed and may cause severe skin and eye irritation or burns. Long-term exposure may cause damage to the central nervous system, lungs, blood, liver, or kidney. Safety glasses and gloves should be worn. It should be used with adequate ventilation and treated as a carcinogen.
- c) Acetic acid is flammable and corrosive. Concentrated acetic acid can cause serious burns, and contact with the eyes can cause severe long-term damage. Safety glasses should be worn. Contact with skin should be avoided.

Step 3:

Synthetic transformation 3:



Experimental 3: (Adapted from a general procedure for the reduction of a nitro group)

A 500 mL 3 necked round-bottom flask was charged with 1 equivalent 3-nitroptalhydrazine (.685 g, 3.31 mmol), .05 equivalents Pd(AcO)₂ (.0364g, .165 mmol), 20 mL dry THF and a magnetic stirring rod. The flask was sealed (with septa) and purged with nitrogen. While purging the flask, a solution of 2 equivalents KF (.384 g, 6.62 mmol) dissolved in 6.6 mL degassed water was added via syringe. 4 equivalents PMHS (.794 mL, 13.24 mmols) were added *slowly* dropwise via syringe. The reaction ran for 30 minutes or until complete as judged by TLC.

Isolation:

After reaction was complete, the flask was opened to air and diluted with 20 mL diethyl ether, and stirred for 5 minutes. The layers were separated and the aqueous layer extracted using diethyl ether. The combined organic layers were filtered through celite (top layer) and neutral alimina (bottom layer) in 1 cm diameter column by flushing with EtOAc. The filtrate was concentrated and subjected to flash chromatography (silica gel, hexanes/EtOAc).

Expected yield: 89%* .7697 g*

Safety, Disposal and Green Issues:

- THF and diethyl ether are known to form peroxides on contact with air, which if allowed to evaporate can leave a mixture of highly explosive compounds. The THF and diethyl ether we have suggested buying contain BHT to inhibit formation of these compounds. They are also an eye and skin irritants, as well as inhalation hazards. Both THF and diethyl ether are highly flammable, and diethyl ether is notably a large explosion hazard, since its vapors can travel considerable distant to a flame or spark source (hot plates included).
- Diethyl ether may be placed in a waste solvent container for disposal.
- THF should be disposed of in a container containing no halogens, strong oxidizing or reducing agents, or in contact with oxygen.
- As a source of fluorine, KF should not be ingested.

*This base for experimental yield is based upon the yield for a nitro arene with a ketone group meta to the nitro group.

Overall Budget:

Chemical	Supplier	Cost	Amt. Needed	Total
1-nitronaphthalene (99%)	Aldrich	\$18.90 / 100g	3.0 g	\$0.57
acetonitrile (99%)	Aldrich	\$43.10 / 1L	5.0 mL	\$0.21
nitric acid (solution, 1M)	Riedel-de Haën	\$32.10 / 1L	69.2 mL	\$2.22
ceric ammonium nitrate	Fluka	\$26.50 / 100g	2.50 g	\$0.66
hydrazine (anhydrous, 98%)	Sigma-Aldrich	\$54.10 / 50g	0.127 g	\$0.14
acetic acid (99.99%)	Sigma-Aldrich	\$24.20 / 25mL	0.661 mL	\$0.64
celite	Fluka	\$34.80 / 1kg	10 g	\$0.35
aluminum oxide (neutral)	Sigma-Aldrich	\$30.30 / 100g	10 g	\$3.03
diethyl ether (anhydrous)	Aldrich	\$291.50/6L	40 mL	\$1.94
tetrahydrofuran (anhydrous, 99.9% with BHT as inhibitor)	Aldrich	\$296.00/12L	20 mL	\$0.49
poly(methylhydrosiloxane)	Fluka	\$32.60/100mL	0.794 mL	\$0.26
palladium(II) acetate	Aldrich	\$40.00/500mg	37.04 mg	\$2.96
ethyl acetate	Sigma-Aldrich	\$389.50/20L	100 mL	\$1.95
Na ₂ CO ₃	Riedel-de Haën	\$43.50/ 5L	2 mL	\$0.04
methanol	Aldrich	\$327.50/ 16 L	20 mL	\$0.41
hydrochloric acid	Fluka	\$26.90/ 1 L	1 mL	\$0.27
potassium fluoride	Sigma-Aldrich	\$55.80/250g	0.384g	\$0.08

Total costs per synthesis: \$16.22

*Because our expected yield for the final step is unknown, these values reflect the highest possible amounts of reagents that may be used.

References:

Step 1:

Rajiah, T.; Chary, K. V. R.; Rao, K. S. R.; Rao, R. N.; Prasad, R. *Green Chem.* **2002**, *4*, 210-212.

Step 2:

Huntress, E. H.; Stanley, L. N.; Parker, A. S. *J. Am. Chem. Soc.* **1934**, *56*, 241-242.

Step 3:

Rahaim, R. J.; Maleczka, R. E. *Org. Lett.* **2005**, *7*, 5087-5090.