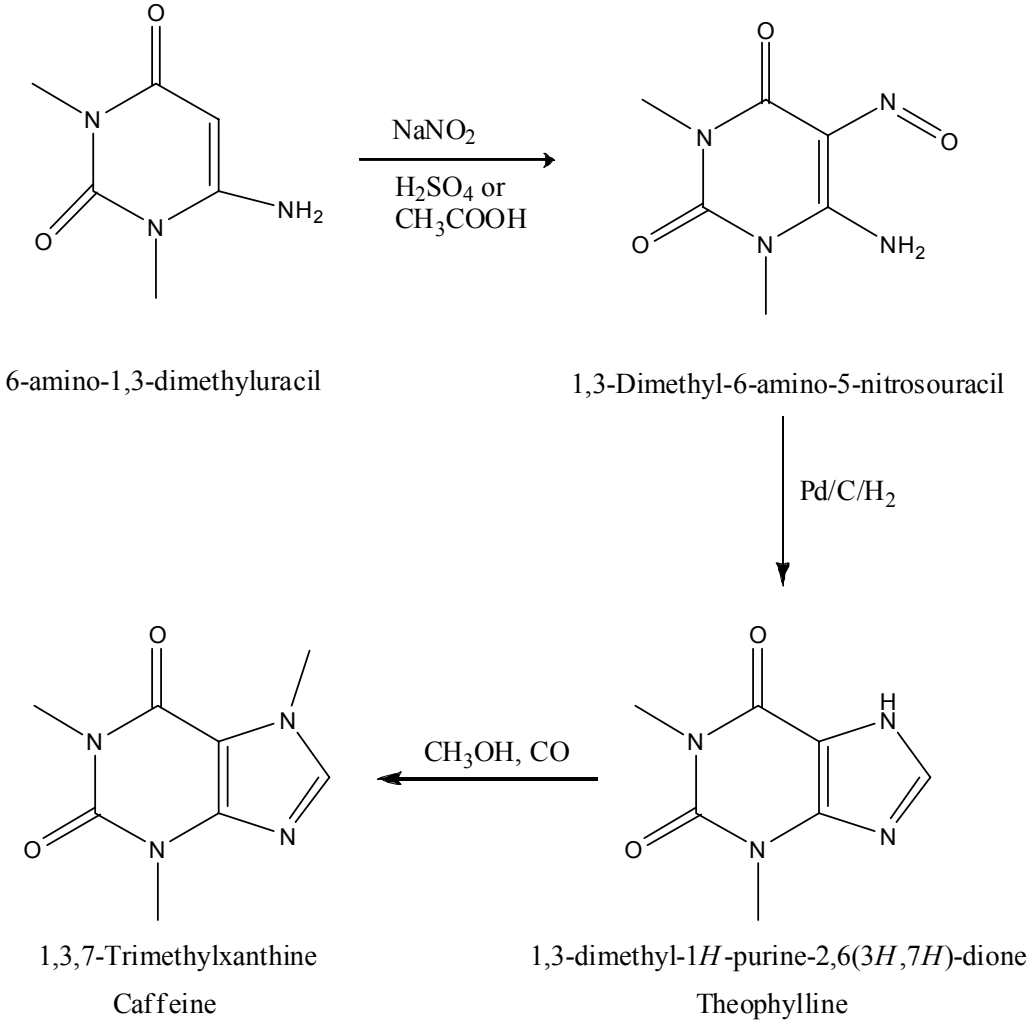
Honors Cup Synthetic Proposal (230 III-Tu PM-W08)

Section: 230
Group Members: Gregory Schmitz, Adam Bowman, Tye Chang

Title: Synthesis of 1,3,7-Trimethylxanthine (Caffeine) from Theophylline

Introduction: Caffeine is a xanthine alkaloid compound that serves as a stimulant in the human body. Despite its label as a drug, caffeine is found in several types of beverages such as coffee, tea, carbonated beverages, and energy drinks. The interest of the synthesis of caffeine is derived from its extreme effectiveness and omnipresence in the university atmosphere. Further, the dependence many students have on caffeine to survive university life brings to light the significance of the simple 3-step synthesis.

Overall Synthetic Reaction Scheme:



6-amino-1,3-dimethyluracil

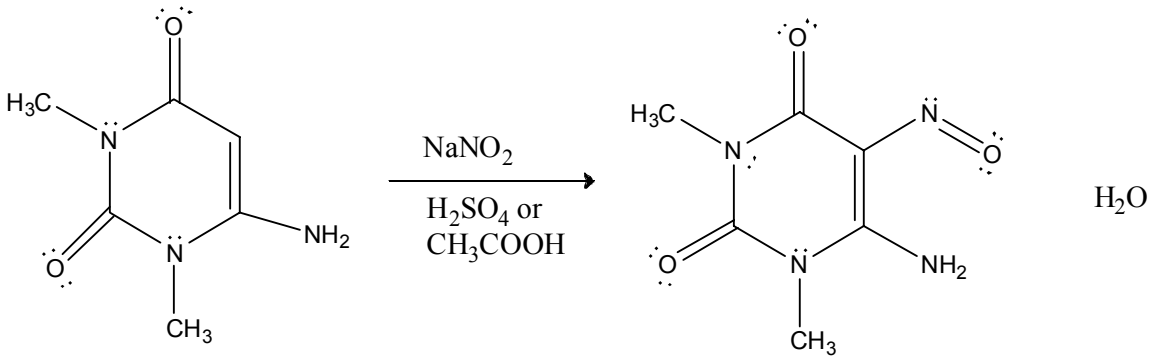
1,3-Dimethyl-6-amino-5-nitrosouracil

1,3,7-Trimethylxanthine
Caffeine

1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione
Theophylline

Step One: Synthetic Transformation of 6-amino-1,3-dimethyluracil to 1,3-dimethyl-6-amion-5-nitrosouracil

Synthetic Step:



6-amino-1,3-dimethyluracil

1,3-Dimethyl-6-amino-5-nitrosouracil

Experimental

Dilute 13.22 g (85.32 mmol) of 6-amino-1,3-dimethyluracil in water (919.5 mL) as it is heated to 50-55 C. Add a solution of sodium nitrite (4.791 g of 100%) in water (281.6 mL) to the mixture. Next, gradually add 10% sulfuric acid (549.5 mL: 58.8 g 100%) or acetic acid solution (136.2 ml of 50%:72 g 100%) over 20-30 min at a temperature of 60-75 C (pH~5.0). A bright red precipitate should develop. Maintain the temperature of 60-75 C for about 10 minutes before cooling it to 20 C. Filter the precipitate and wash it three times with cold water (214 mL). Allow to air dry. This produces approximately 11.07 g of 1, 3-dimethyl-6-amino-5-nitrosouracil (63.99 mmol), approximately a 75% yield.

Safety, Disposal, and Green Issues:

(1) 6-amino-1,3-dimethyluracil – not classified as hazardous

(2) Sodium Nitrate – toxic, oxidant, and harmful to the environment. Make sure it is kept sealed when not in use.

(3) Sulfuric Acid – corrosive, non-flammable. Short exposure could cause injury. Do not place in a high temperature area, the chemical undergoes violent chemical changes. Handle with care.

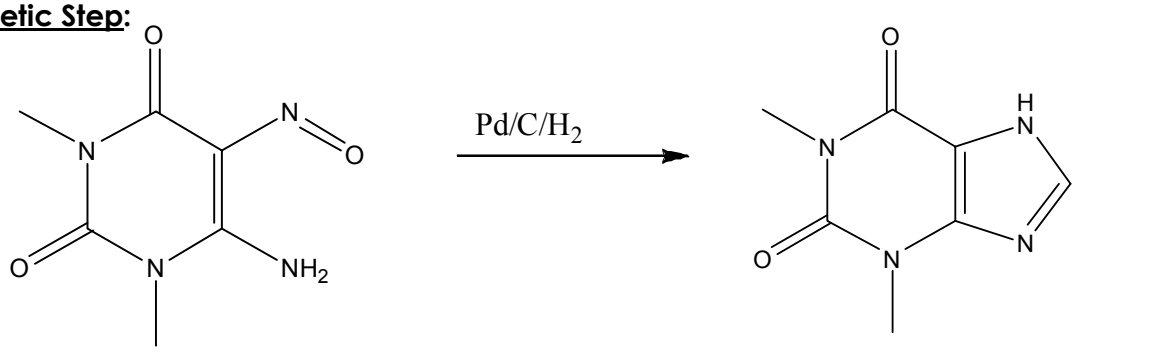
(4) Acetic Acid – prolonged exposure can be harmful. Only flammable when heated to 43 C. Also it can undergo chemical changes if heated or exposed to water. Handle with care.

Citations

Abramova, E. I.; Kuteliya, A. V.; Feklistova, V. F. *Pharm. Chem. J.* **1978**, *12*, 97-98.

Step Two: Synthetic Transformation of 1,3-dimethyl-4-amino-5nitrosouracil to Theophylline

Synthetic Step:



1,3 dimethyl-4-amino-5-nitrosouracil

1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

Theophylline

Experimental

11.77 g (63.99 mmol) of 1,3-dimethyl-4-amino-5-nitrosouracil (41% water content) were combined with 40 ml of water and 5 g of 5% palladium/charcoal catalyst (precipitated via alkaline reactions). Concentrated NaOH was added to the reaction mixture to adjust the pH to 9. The resulting suspension was hydrogenated under a hydrogen pressure of 3 bar, while stirring, within a temperature range of 30 to 50 degrees Celsius. After the uptake of Hydrogen had ended, the reaction mixture was cooled to 25 C. 2.04 g of Formic Acid (44.40 mmol) was added, and then the catalyst was filtered off. 1.278 g more of formic acid was added to the filtrate and the mixture was left to finish reacting at 85 degrees Celsius for 40 minutes. After 40 minutes, the mixture was combined with 3.321 g (44.82 mmol) calcium hydroxide suspension, after which the calcium salt of the theophylline was precipitated. This precipitate was filtered off, washed with 30 ml of water. The isolated resultant was dried for about 12 hours at 60 C in a circulating air dryer. The resulting compound is .6532 g of Theophylline (3.265 mmol) approximately a 79% yield.

Safety, Disposal, and Green Issues:

(1) Palladium – a stable metal that is generally not toxic to humans, except if the palladium is injected into the skin or inhaled in large quantities, avoid direct contact to skin.

(2) Sodium Hydroxide – can cause chemical burns and blindness, when in use make sure goggles are on and handle with care.

(3) Formic Acid – corrosive; should not make contact with the skin and especially the eyes. Also inhalation should be avoided. Be sure to handle in a hood or ventilated area.

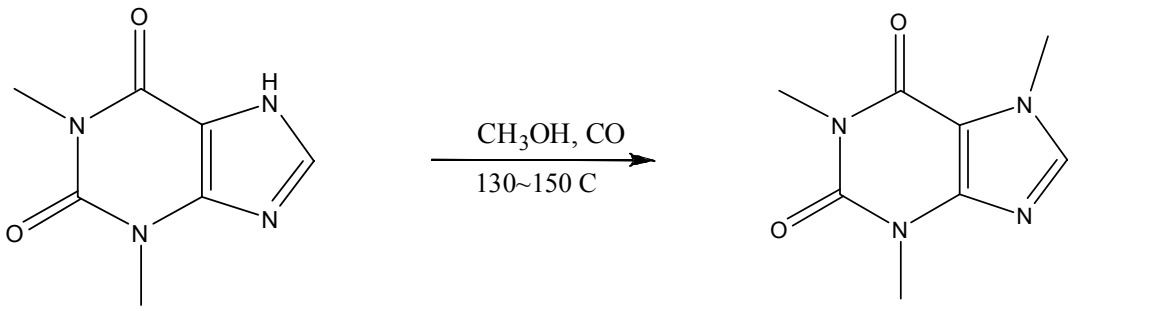
Citations

Bhat, S. T.; Nagasampagi, B. A.; Sivakumar, M. *Chemistry of Natural Products*, New York: Springer, 2004; pp. 314.

Dach, Rolf. "Process of preparing 1,3-dimethyl-4,5-diaminouracil." U.S. Patent 5,510,484. 23 April 1996.

Step Three: Synthetic Transformation of Theophylline to Caffeine

Synthetic Step:



1,3-dimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione
Theophylline

1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione
Caffeine

Experimental

The .6352 grams theophylline (3.267 mmol) collected was placed in an excess methanol solution (81.38 mmol) and heated (130~150 C) in stirred autoclave under a CO pressure of 50 bar. After approximately 20 hours, the mixture was placed inside a distillation flask and heated to separate methanol and methyl formate from the yielded caffeine-containing solution. The obtained product yield should be approximately 97% and the caffeine could be further extracted from the resulting residue using ethyl acetate. The success of extraction could be confirmed through Thin Film Chormatography and H'NMR.

Safety, Disposal, and Green Issues:

(1) Caffeine – harmful, avoid direct contact with skin, do not swallow, do not inhale. Caffeine should be handled under the hood/or other ventilated areas.

(2) Theophylline – avoid contact with skin and eyes, do not swallow, do not inhale. If it is spilled, it should be disposed into a sealable container (may need to moisten first to prevent dusting)

(3) Methanol (CH_3OH) – toxic and flammable, keep under the hood when in use. Avoid contact with skin and do not inhale fumes.

(4) Carbon Monoxide (CO) – highly toxic and flammable, do not inhale and avoid prolonged exposure to the fumes. Carbon monoxide must be handled in a well ventilated area.

Citations

Bott, Kaspar. "Preparation of Caffeine." U.S. Patent 4,380,631. 19 April 1983.

Overall budget:

Chemical	**Supplier**	**Cost**	**Amt. Needed**	**Total Cost**
6-Amino-1,3-dimethyluracil	Sigma Aldrich	$0.52/gram	13.22 grams	$ 6.87
sodium nitrite	Sigma Aldrich	$3.01/gram	4.791 grams	$ 14.42
Acetic Acid	Sigma Aldrich	$28.90/Liter	.1362 L	$ 3.94
Palladium on activated charcoal	Sigma Aldrich	$4.81/gram	5 grams	$ 24.05
Calcium Hydroxide	Sigma Aldrich	$0.07/gram	3.321 grams	$ .23
Formic Acid	Sigma Aldrich	$0.06/gram	2.04 grams	$ .12

Total Cost per Synthesis: $49.63