Research In Green Organic Chemistry: The Design of Greener Undergraduate Labs

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Outline

- Green Chemistry
- Research Objectives
- Green Considerations
- My Research
  - Greener Synthesis of Creatine
  - Green Chlorination of Vanillin
- Experimental Results
- Green Aspects

Green Chemistry

- The utilization of a set of principles that reduces or eliminates the use and/or generation of hazardous substances in the design, manufacture, and application of chemical compounds.
- The goal is to make reactions safer, more efficient, and more cost effective while minimizing personal and environmental harm.

My Research Objectives

- Develop greener organic chemistry labs that can be performed safely and effectively by undergraduate students.
- Labs must incorporate organic chemistry lecture material.
- Labs must meet the overall goals of Green Chemistry.

Green Considerations

- Replace hazardous reagents with safer renewable reagents
- Minimize or eliminate the generation of hazardous waste and products
- Avoid auxiliary substances, such as solvents, whenever possible.
- Use reagents catalytically rather than stoichiometrically

Green Considerations Continued…

- Minimize energy use
- Maximize the incorporation of all starting materials used into the final product (Atom Economy).
- Develop procedures that can be performed on an open bench top
- Generate products and by-products that can be recycled or reused

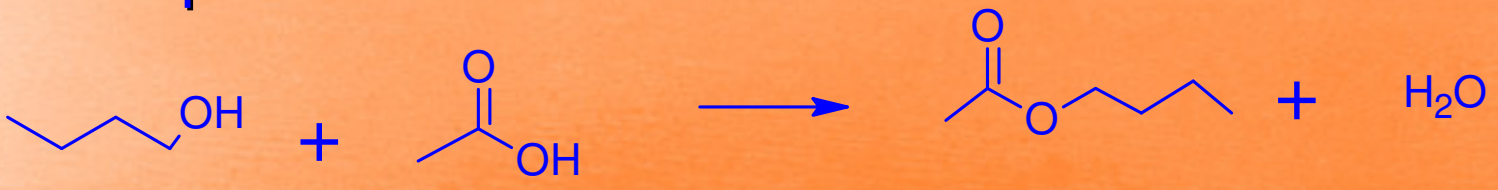
Atom Economy

- Atom Economy= $\frac{\text{MW of Product}}{\text{MW of all Reagents}} \times 100\%$

- The incorporation of as many of the atoms used in the reagents into the final product.

Atom Economy

- For Example…



1-butanol
FW 74.12

acetic acid
FW 60.05

n-butyl acetate
FW 116.15

FW 18.02

- $\frac{116.15g\ C_6H_{12}O_2}{(74.12g\ C_4H_{10}O + 60.05g\ C_2H_4O_2)} \times 100\% = 86.6\%$

- By-Product is H_2O accounting for 18.02g or (13.4%)

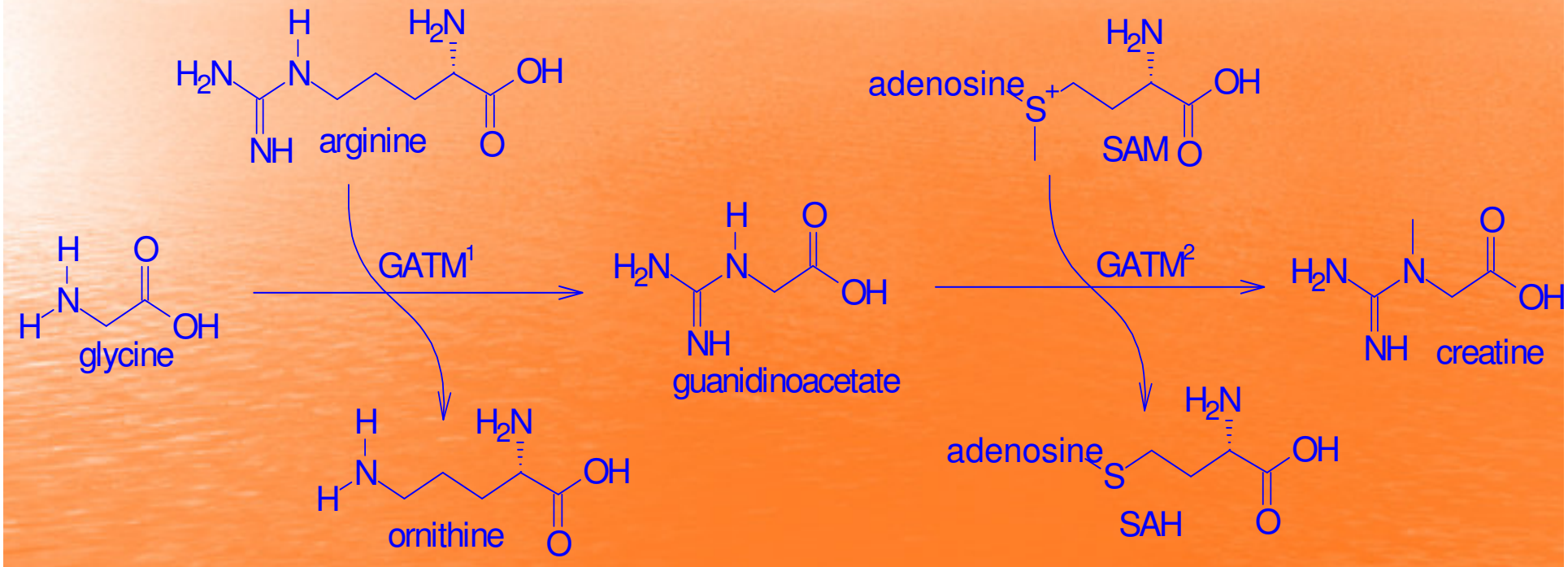
Identity of By-Product

- Best Circumstance: No by-products if possible
- Generate low molecular weight by-products (ex. H_2O)
- By-products must be evaluated for:
  - Toxicity
  - Potential hazards (volatile, Cl_2)
  - Ease and appropriateness of Disposal (drain, vent to atmosphere, incinerate)

A Greener Synthesis of Creatine

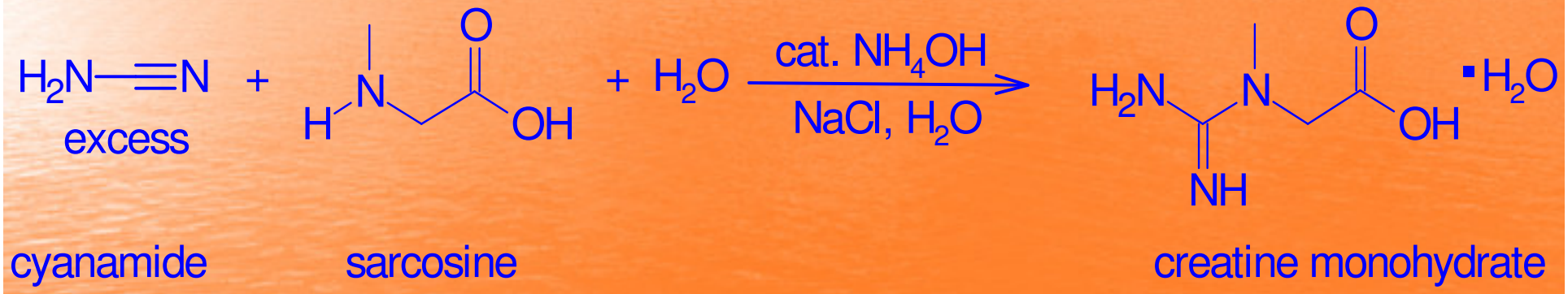
- Nitrogenous organic acid that is synthesized naturally by the human body
- Found primarily in skeletal muscles
- Fundamental to the energy metabolism of muscle cells
- Currently one of the best-selling sports supplements: Annual U.S. Sales exceed $400 Million in powder and pill form

Biological Pathway of Creatine



GAMT[1] - Guanidinoacetate N-methyltransferase; GAMT[2] - Glycine amidinotransferase;
SAM - S-adenosyl methionine; SAH - S-adenosyl homocysteine

Typical Synthesis of Creatine



cyanamide sarcosine creatine monohydrate

Common Creatine Impurities

- Dicyanodiamide

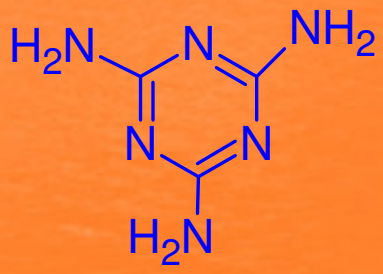
Non toxic – fertilizers, Flame retardant, cleaning Compounds

- Sodium Chloride

NaCl

Table salt

- Dihydrotriazine



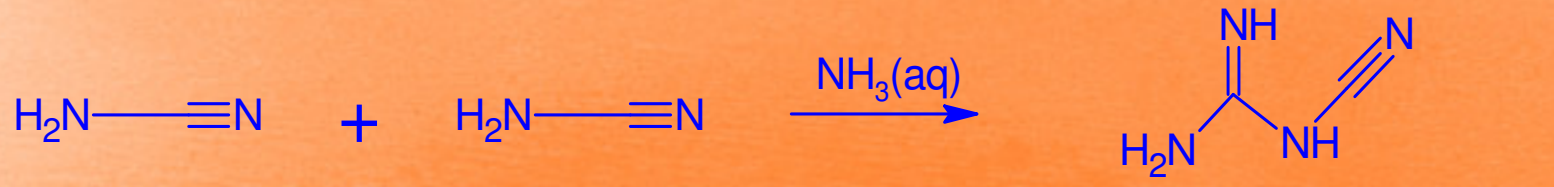
Toxicity unknown- in Same family of chemicals As melamine (poisonous)

- Creatinine

Non toxic- metabolized Waste product of creatine

Formation of Impurities

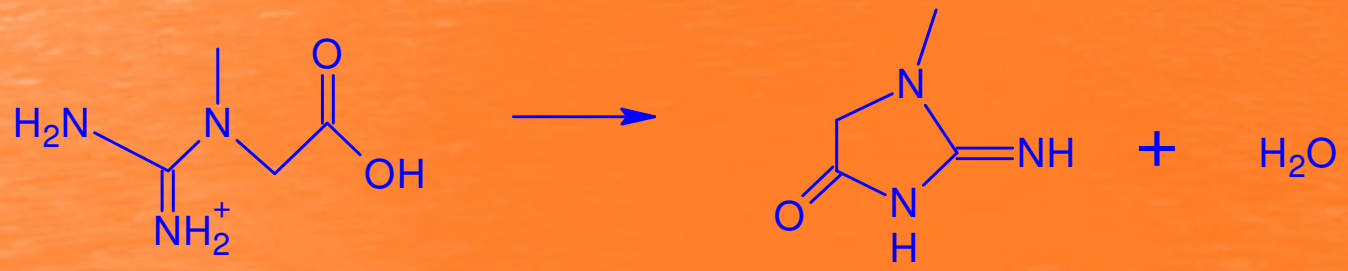
- Dicyanodiamide



cyanamide cyanamide dicyanodiamide FW=84.08

mp 209.5°

- Creatinine



creatine creatinine

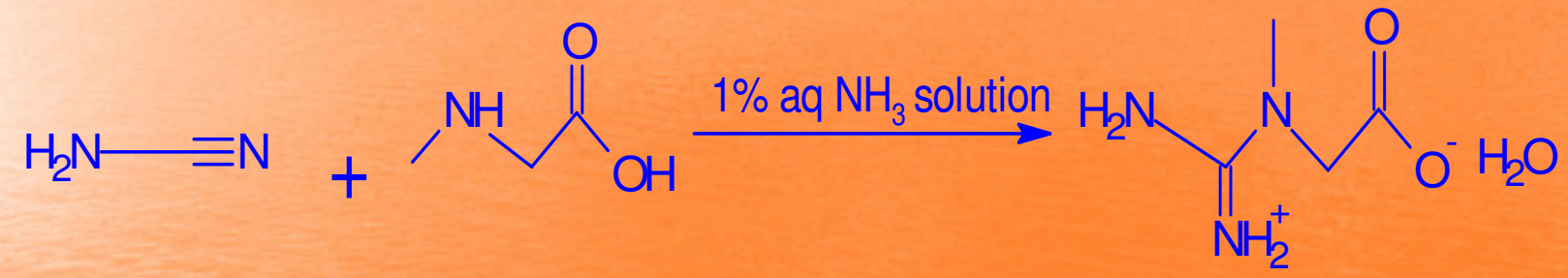
Industrial Impurities

	Creatinine	Dicyandiamide	Dihydrotriazine	Sodium	Percentage of Composition
German Manufacturer	< 50 ppm	< 20 ppm	n.d.	trace	
US Manufacturer #1	190ppm	400ppm	410ppm	750ppm	
US Manufacturer #2	300ppm	100ppm	40ppm	no data	
US Manufacturer #3	2500ppm	300ppm	90ppm	no data	
Chinese Manufacturer #1	1500ppm	2300ppm	n.d.	no data	
Chinese Manufacturer #2	100ppm	18000ppm	n.d.	no data	1.80%
US Distributor #1	50ppm	20ppm	n.d.	trace	
US Distributor #2	520ppm	40ppm	24ppm	280ppm	
US Distributor #3	220ppm	120ppm	60 ppm	1250ppm	
US Distributor #4	3000ppm	2000ppm	16ppm	220ppm	
US Distributor #5	320ppm	60ppm	60ppm	no data	
US Distributor #6	50ppm	34000ppm!	72ppm	530ppm	3.40%
US Distributor #7	70ppm	30ppm	300ppm	no data	
US Distributor #8	210ppm	80ppm	160ppm	no data	
US Distributor #9	50ppm	20ppm	n.d.	trace	
US Distributor #10	180ppm	80ppm	176ppm	360ppm	
US Distributor #11	1480ppm	80ppm	30ppm	no data	

Experimental Variables?

- Evaluation of Reagents
  - Eliminate excess cyanamide
- Eliminate use of NaCl
- Eliminate use of concentrated NH_4OH catalyst
- Could procedure be simplified?

A Greener Synthesis of Creatine



cyanamide FW= 42.04 sarcosine FW= 89.09

creatine monohydrate FW=149.16

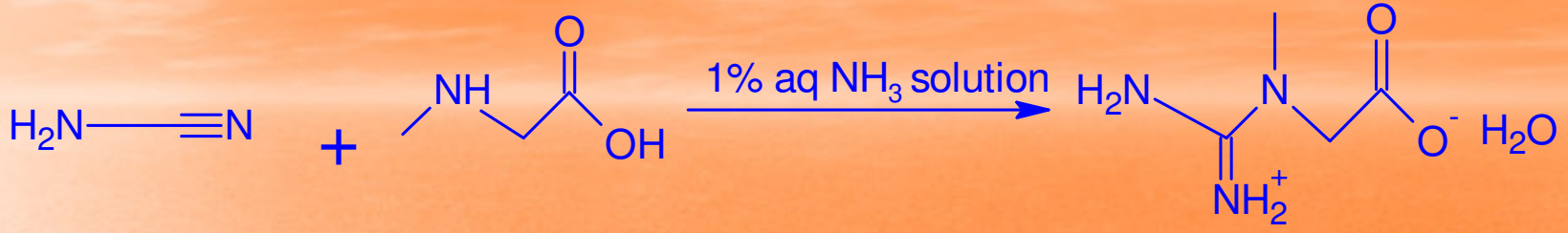
Optimized Procedure

- 10 mmol cyanamide : 10 mmol sarcosine
- 2 mL of 1% aqueous ammonia solution
- Combined and stirred for 1 hour
- Allowed solution to sit undisturbed for 1 day
- Collected crystals by vacuum filtration

Experimental Creatine Results

- Average Percent Yield: 97%
- Average Decomposition: 291.5 ^{o}C
- Product Identity was successfully confirmed via IR Spectroscopy and Nuclear Magnetic Resonance (NMR)

Green Aspects



cyanamide FW= 42.04 sarcosine FW= 89.09

creatine monohydrate FW=149.16

- Safe Reagents
- Eliminate Excess Cyanamide
- Reusable Aqueous Solvent
- Dilute & Reusable Catalyst
- Absence of Fume hood
- High Purity Product
- 100% Atom Economy
- Minimal Energy Needed

Undergraduate Procedure

- Used optimized procedure to develop undergraduate procedure
- Facilitated undergraduate experiment
- Collected and analyzed undergraduate data

Undergraduate Lab Results

- Average Percent Yield = 76% (n = 12)
- Average Decomposition Point = 287 ^{o}C
- IR Spectrum confirmed product identity and purity
- Lab Time: 1.5 hours (3 half hour time slots)

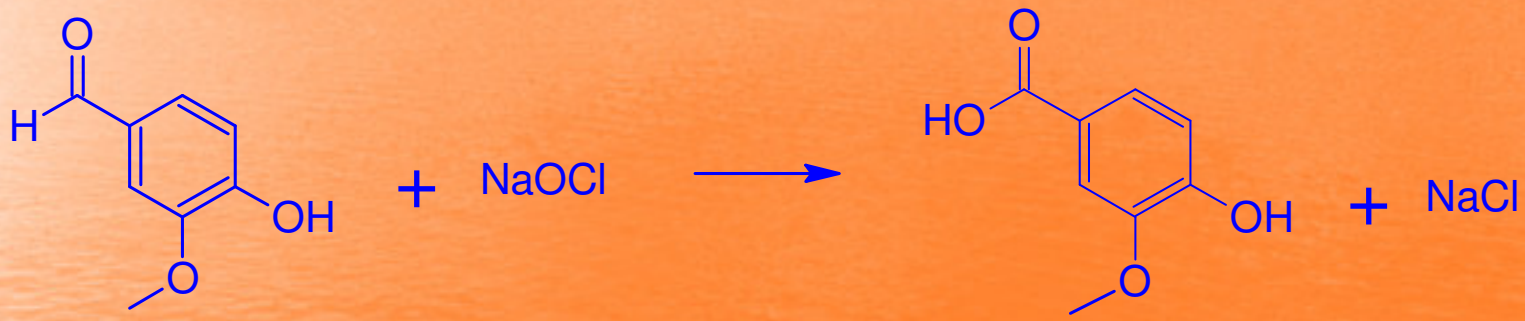
Conclusion

- Data Gives Evidence that Creatine Procedure can be performed safely and effectively in an undergraduate organic lab.
- Procedural evaluations conclude that the synthetic methodology has been significantly improved for overall greenness.
- **A Win : Win Situation** is a **SUCCESS** in **Green Chemistry!**

  (Performing safe, efficient reactions while minimizing environmental harm)

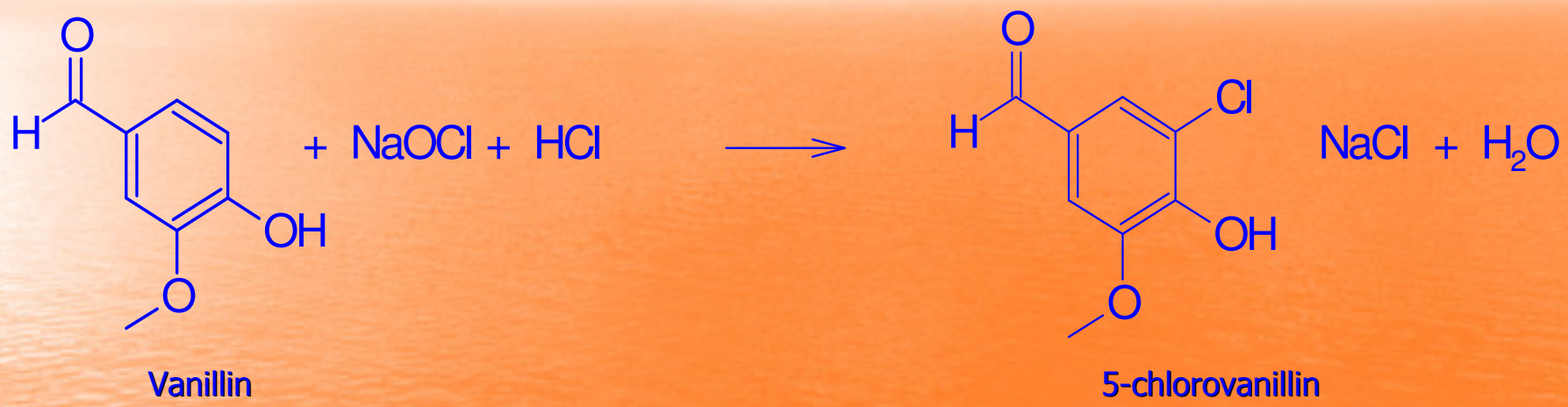
Second Research Interest

- Develop a Bleach Oxidation of Vanillin



- Instead, accidentally discovered a novel chlorination of vanillin

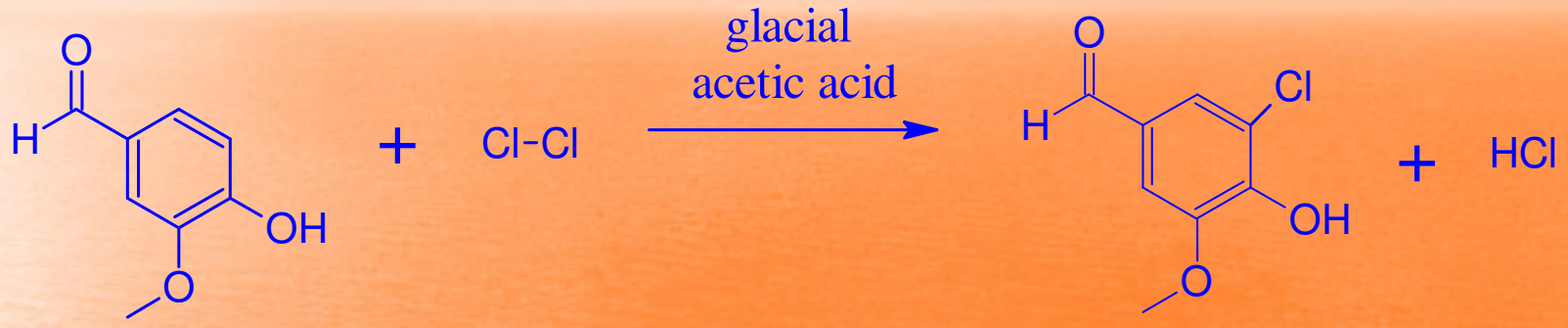
A Novel Chlorination of Vanillin



Vanillin

5-chlorovanillin

Traditional Aromatic Chlorination (1929-Present)

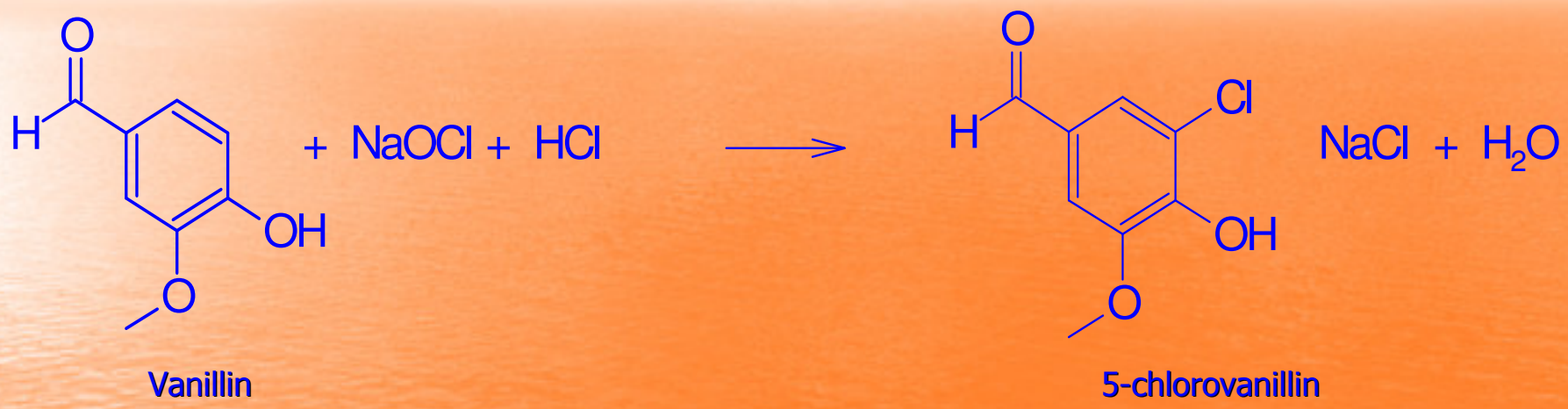


vanillin FW = 152.12

5-chlorovanillin FW = 186.59

- Elemental Chlorine (poisonous green gas)
- Fuming Hydrochloric acid
- Difficult Solvent to work with
- Fume Hood Required
- Overall Nasty Reaction

My Greener Chlorination of Vanillin



Vanillin

5-chlorovanillin

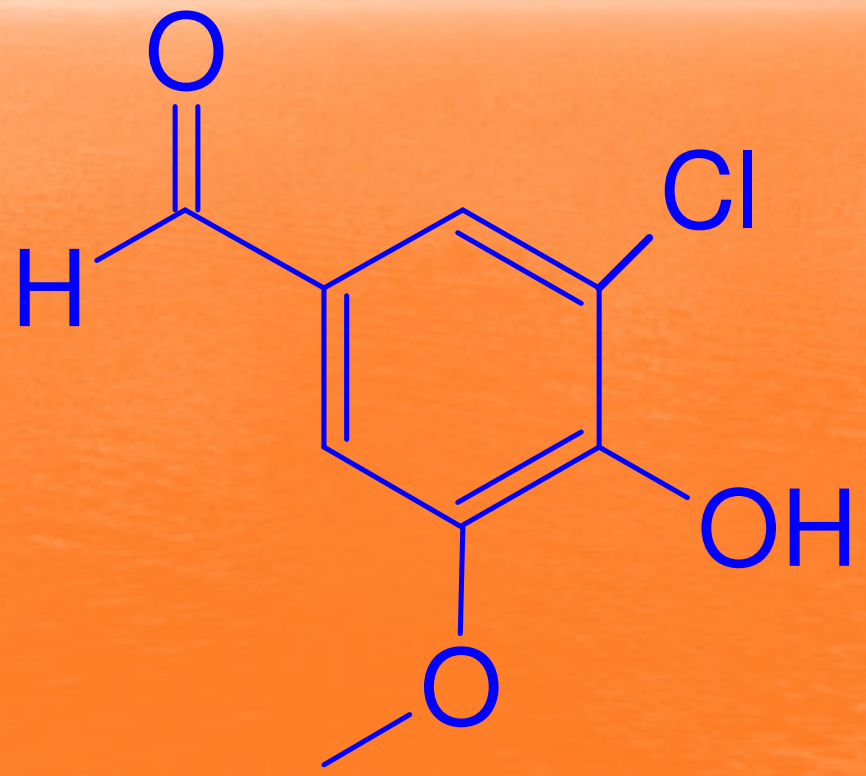
- Household Bleach (NaOCl) vs. Cl_2
- Benign solvent: ethanol vs. glacial acetic acid
- Fume hood not needed vs. fume hood essential
- Inert by-products: NaCl, Water vs. Fuming HCl

Bleach as a Chlorinating Agent[1]

- Finally, found a paper in a 1946 Canadian Chemical Journal
- Rediscovered bleach had been used as a chlorinating agent for vanillin once before
- However, never used again in any chemical literature

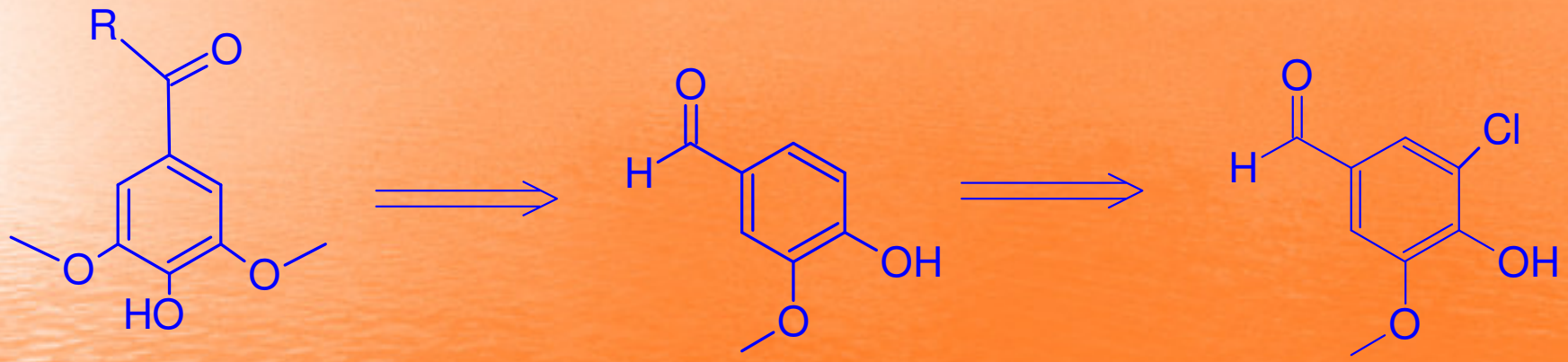
[1] Primary literature reference: Chlorination by Aqueous Sodium Hypochlorite, Hopkins, C.Y. and Chisholm, M.J. *Can. J. Res. B*, **1946,** *24*, 208-210.

5-chlorovanillin



- Chlorine substituent creates a versatile reagent with 4 sites for further elaboration
  - aldehyde
  - aromatic chloride
  - phenol
  - ether

Renewable Starting Material



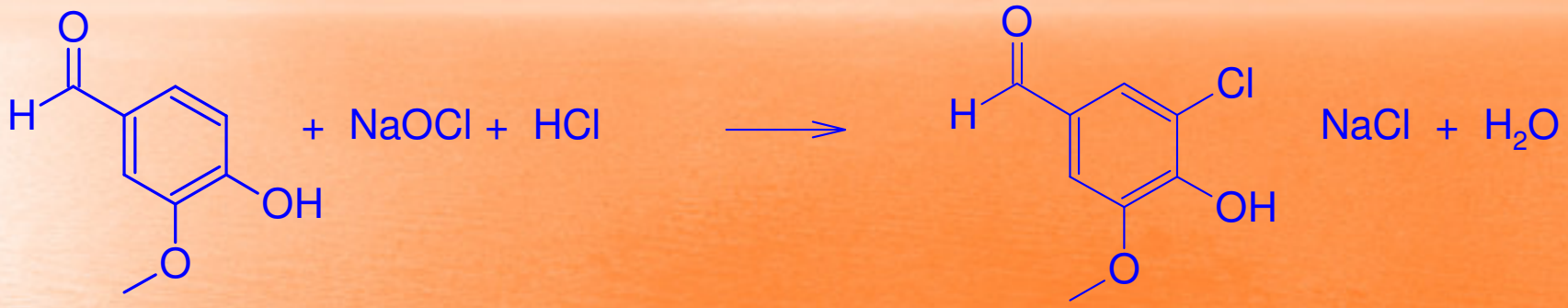
Waste Product (Lignin monomer)

vanillin

5-chlorovanilln

- Vanillin derived from renewable sources (Lignin from wood pulp)

Optimized Procedure



- 1.52g (10 mmol) Vanillin dissolved in 10 mL EtOH
- 15 mL 0.73 M NaOCl added drop-wise
- Acidic Workup
- Collect crystals by Vacuum Filtration

Experimental Chlorination Results

- Average Percent Yield: 95.0%
- Average Melting Point: 161-165 °C (crude)
- Successfully confirmed product identity via IR Spectrum and NMR
- Atom Economy: 70.9%

Green Aspects

- Renewable starting material
- Cl_2 Replaced with NaOCl (Household Bleach)
- Green Solvent
- Benign By-products
- Absence of Fume Hood
- Minimal Energy Needed
- Good Atom Economy
- High Percent Yield

Undergraduate Procedure

- New chemistry was developed into an undergraduate procedure
- Facilitated undergraduate experiment
- Collected and analyzed undergraduate data

Undergraduate Lab Results

- Average Percent Yield = 78.0% (n=12)
- Melting point and IR spectrum confirmed product identity and purity
- Estimated Lab time = 1.5 hours

Conclusion

- Data Gives Evidence that the Chlorination of Vanillin procedure can be performed safely and effectively in an undergraduate organic lab.
- Procedural evaluations conclude that the synthetic methodology has been significantly improved for overall greenness.
- **A Win : Win Situation** is a **SUCCESS** in **Green Chemistry!**

(Performing safe, efficient reactions while minimizing environmental harm)

Acknowledgements

- Special Thanks:
  - Dr. Carl Lecher
  - CHE 306
  - Marian College and the School of Mathematics and Sciences
  - CHE 498 Group

QUESTIONS…