

A Greener Synthesis of Creatine

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Chemical Concepts

Addition to nitriles, vacuum filtration, melting point determination

Green Lessons

Benign solvents, reduction of excess reagents, safer reaction conditions, 100% atom economy, high reaction efficiency, benign product

Estimated Lab Time

Setup = 1 hour

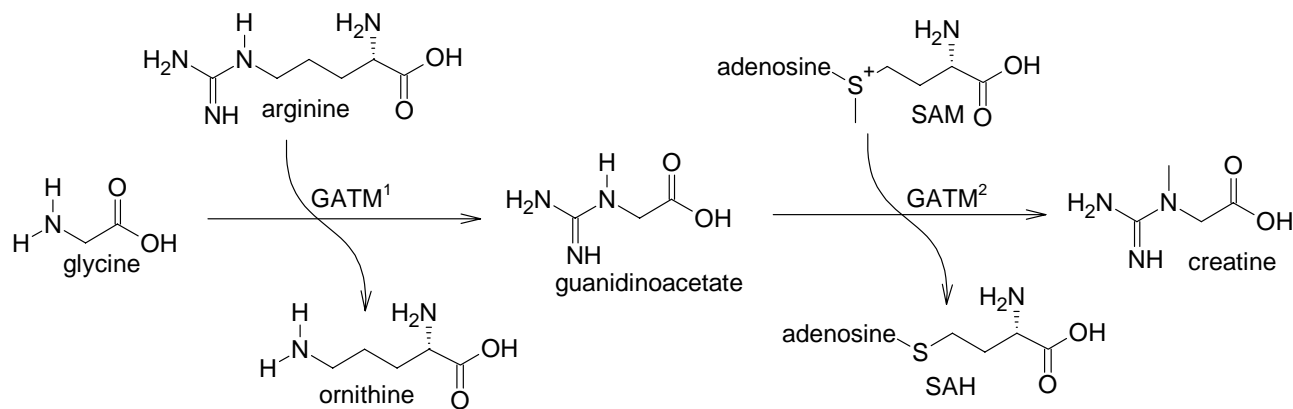
Workup = 1 hour

Scenario

Max Maximus, a chemist and local power lifting champion, has approached your company to discuss a business proposition. After reading an article in *Mega Muscle Magazine* about low quality creatine being sold in health and nutrition stores, Max is interested in the possibility of partnering with you on the development of an improved creatine synthesis.

Background

Creatine is a nitrogenous organic acid that is synthesized naturally by the human body. It is produced in the liver, kidneys, and pancreas from the amino acids glycine, arginine, and methionine (see Scheme 1), and may also be obtained from foods such as meats and fish. Creatine is found primarily in skeletal muscle and is fundamental to the energy metabolism of muscle cells. In skeletal muscle creatine exists in equilibrium with phosphocreatine. Phosphocreatine acts as an ATP reservoir. The reverse reaction provides a rapid source of ATP to the muscle cell, and appears to enhance anaerobic capacity, aerobic recovery, and protein synthesis. For these reasons, creatine is used by athletes both to increase muscle mass and to enhance performance in high-intensity exercise.



GAMT¹ - Guanidinoacetate N-methyltransferase; GAMT² - Glycine amidinotransferase;

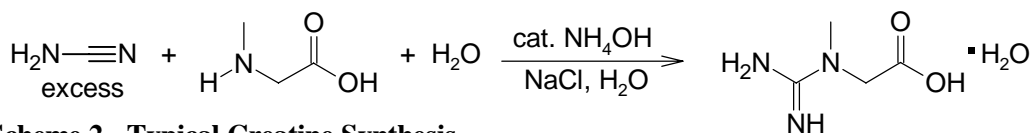
SAM - S-adenosyl methionine; SAH - S-adenosyl homocysteine

Scheme 1. Biological Pathway for the Synthesis of Creatine

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In the last 30 years, athletes and body builders have begun to take supplemental creatine in the form of powder or a pill in order to maximize the amount of creatine available to their muscle cells. Creatine is currently one of the best-selling sports supplements on the market with annual U.S. sales exceeding \$400 million. Companies worldwide have developed synthetic procedures to make creatine or creatine derivatives to meet this demand. Since creatine is a nutrient and not a drug, it is not regulated by the Food and Drug Administration. Therefore, companies do not have to reveal or specify the synthetic procedure that is used. However, there is a common procedure that is thought to be used by many companies as an industrial procedure for the production of creatine monohydrate (see Scheme 2). Creatine is commonly synthesized from sarcosine and cyanamide (used in excess) in the presence of concentrated ammonium hydroxide (NH₄OH), which contains about 28-30 percent ammonia in solution.³ This procedure also uses two equivalents of NaCl as an additive to aid in the precipitation of the product.

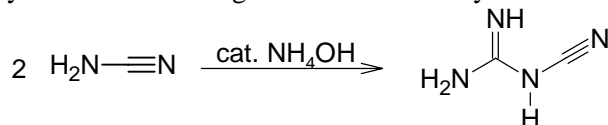


Scheme 2. Typical Creatine Synthesis

Creatine can also be prepared by heating sodium sarcosinate and cyanamide in a mixture of water and organic solvent.⁴

Background - Impurities

A common impurity found in creatine monohydrate is dicyanodiamide. While dicyanodiamide is generally not considered to be toxic in humans, there are no known benefits. Dicyanodiamide is typically prepared by the ammonium hydroxide catalyzed dimerization⁵ of cyanamide in water (Scheme 3). These are the same reaction conditions used for the creatine synthesis. It would be anticipated that excess cyanamide remaining from the creatine synthesis would dimerize to form dicyanodiamide as an impurity.



Scheme 3. Dimerization of cyanamide

Another impurity occurring in the creatine monohydrate is sodium chloride. Sodium chloride is introduced to the reaction as an auxiliary reagent to aid in the precipitation of creatine monohydrate. Presumably the sodium chloride is trapped in the growing crystalline lattice. While neither impurity is necessarily hazardous, consumers are still purchasing inferior creatine monohydrate.

Greening the Chemistry

As a green chemist, you should identify three ways which could potentially improve both the greenness and quality of the creatine synthesized by this method. The first is to reduce the amount of cyanamide used from two equivalents to one equivalent. Not only would this improve the effective mass yield of the reaction, it should greatly reduce the generation of dicyanodiamide. The second is to eliminate use of NaCl. This would also improve the effective mass yield of the reaction, as well as eliminate the presence of any sodium chloride in the procedure. The third would be to eliminate use of concentrated ammonium hydroxide, which presents a host of safety problems, including causing severe skin irritation, skin burns, and severe irritation to the upper respiratory tract. Replacing concentrated ammonium hydroxide with household ammonia (which can be further diluted) would eliminate these safety concerns and the need for a fume hood.

³ Smith, A. L., Tan, P. *J. Chem. Ed.* **2006**, 83, 1654-1656.

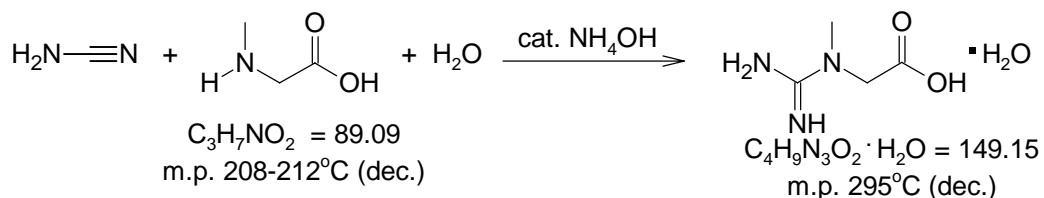
⁴ Weiss, Stefan, Krommer, Helmut. United States Patent 5,719,319.

⁵ A dimerization is a reaction linking two of the same type of molecules.

In the lab

Our primary goal is to see if these modifications can be done without dramatically lowering yields. In this experiment, you will perform the modified procedure and compare your results to the traditional procedure.

Scheme 4. Reaction Scheme



Reaction Table

Name	Formula	Weight	eq	mmol	wt / vol
cyanamide		42.04	1.00	10.0	0.42 g
sarcosine		89.09	1.00	10.0	0.89 g

Safety Precautions

Cyanamide: Cyanamide is toxic. Wear gloves when handling.

Experimental Procedure

Reaction

1. Obtain between 0.40 and 0.44 g of cyanamide. Record the mass directly into your notebook to the maximum accuracy of the balance. Add to either a 10 mL round bottom flask or a 20 mL scintillation vial.
2. Obtain between 0.85 and 0.93 g of sarcosine. Record the mass directly into your notebook to the maximum accuracy of the balance. Add to the reaction vessel.
3. Add 2 mL of dilute aqueous ammonia.^{6,7} Add a stir bar, cap, and dissolve with stirring.
4. Stir for 60 minutes, or until the solution becomes chalky white. Remove from the stir plate and allow the flask to set undisturbed for at least 24 hours to allow the precipitate to form.
5. Fill out your reaction table by calculating the mmol and equivalents of reagents used based on your masses. Show your calculations under the reaction table.

Day # 2 – Isolation of the Product

6. Collect the solid by vacuum filtration. Use small portions (~1 mL) of **ice-cold** DI water to aid the transfer of the solid into the filter funnel and to wash the product. With the vacuum applied, allow the solid to dry on the vacuum for about two minutes. Save your solid. Place your filtrate in the container labeled AQUEOUS FILTRATE.
7. Air dry product to a constant mass in the fume hood for at least 24 hours.
8. Weigh your dried product. Make sure to account for the weight of the filter paper.

⁶ Prepared by diluting new household ammonia (usual concentration 5-10% ammonia) by a factor of five. Reduce the dilution for older ammonia. Watch out for surfactants and other additives in the ammonia!

⁷ Safety note – As a general safety rule, solutes should be added to solvents. The resulting solution should go from dilute to more concentrated. This is because the solvation process for some compounds can be violently exothermic.

Characterization and Calculations

9. Determine the theoretical yield and percent yield for the reaction.
10. Determine the melting point range for your creatine, as well as for a sample of creatine made from the traditional procedure.
11. Generate an IR spectrum for your creatine. Assign the major peaks for the spectrum in your notebook. Also, submit your spectrum when you turn in your notebook pages.
12. Confirm the identity of your product.

Disposal

13. When you are satisfied with your data and calculations, place your product in the container labeled CREATINE. The instructor will save this compound for future use.

Assignment

In addition to the lab notebook, answer the following questions:

1. Propose a valid mechanism for the synthesis of creatine. Make sure to draw the reaction intermediates (including any charges) and to show the flow of electrons with curved arrows.
2. Calculate the atom economy for the reaction.

$$\text{Atom economy} = (\text{MW desired product} / \text{combined MW of all reagents}) \times 100\%$$

3. Would you consider this reaction to be atom efficient? Justify your answer.
4. Calculate the effective mass yield. Ignore the mass of the aqueous ammonia.
$$\text{Effective mass yield} = (\text{mass of desired product obtained} / \text{combined mass of all reagents used}) \times 100\%$$
5. Identify the possible components of the aqueous filtrate.
6. What is the solvent for this reaction?
7. Does the reaction need to be performed with the protection of a fume hood?
8. Compare the melting point of your sample to the melting point of the sample of creatine made from the traditional procedure. What does this indicate with regards to the purity of the two samples?
9. Did you meet the objectives for this reaction? Explain why or why not.

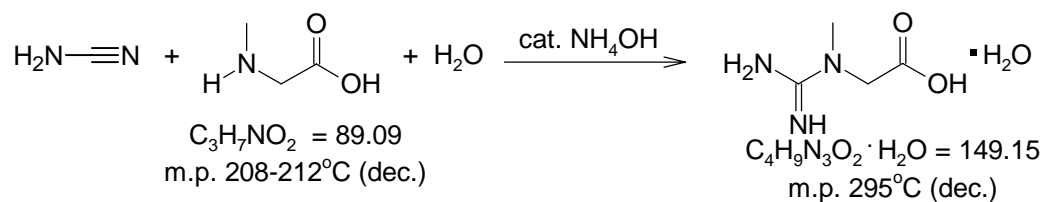
Result Submission Form

Lab Title: A Greener Synthesis of Creatine

Name: _____

Semester and Year: _____

Reaction Scheme:



Your Reaction Table

Name	Formula Weight	density	eq	mmol	wt / vol
cyanamide	42.04	--			
sarcosine	89.09	--			
<i>other reagents not needed in this table</i>					

Your Results

Mass of Product	
Theoretical Yield	
% Yield	
Melting point range	
<i>other values not needed in this table</i>	

Explain any reasons why your yield would be lower than expected:

Make at least 1 suggestion for improving the lab: