

Synthesis of Creatine – A High School Procedure

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Chemical Concepts

Organic chemistry, biological chemistry, catalysis, addition reaction

Green Lessons

Benign solvent, reaction optimization, 100% atom economy, high reaction efficiency (no excess reagent), benign product

Laboratory Techniques

Gravity / vacuum filtration, optional melting point determination

Indiana Academic Standards for Chemistry 1

Includes: C.1.1, C.1.2, C.1.3, C.1.4, C.1.8, C.1.9, C.1.12, C.1.13, C.15, C1.21, C1.27, C.1.35, C.1.44, C.1.45

Estimated Lab Time

Day one: 30 minutes (set up reaction)

Day two: 30 minutes (isolation of creatine)

Synopsis:

A simple procedure for synthesis of creatine. The procedure is well optimized, and to our knowledge represents the greenest route to creatine.

Material List (per student):

Cyanamide (0.42 g)

Sarcosine (0.89 g)

Dilute ammonia solution³ (2 mL) – see footnote below

Small (10 -20 mL) reaction vessel (could be a flask, beaker, or vial)

Stir plate

Distilled or de-ionized water

Ice

Filtration device (gravity filtration is acceptable, but vacuum filtration is superior)

Safety Precautions:

Cyanamide is toxic. It is recommended to wear gloves when handling the cyanamide. It is suggested that the instructor pre-weigh the cyanamide into the reaction vessel. This would minimize student contact with cyanamide, and reduce time and log jams at balance stations. The participants will then simply add additional materials to the known mass of cyanamide.

Questions for Instructors:

Are the estimated lab times accurate? Are the scenario and background sections useful to retain? Please share your experiences with us!

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³ 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!

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Scenario

Max Maximus, a chemist and local power lifting champion, has approached you 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, 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.

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. Creatine is commonly synthesized from sarcosine and cyanamide (used in excess) in the presence of concentrated ammonium hydroxide (NH_4OH), which contains about 28-30 percent ammonia in solution. This procedure also uses two equivalents of NaCl as an additive to add in the precipitation of the product.

Background - Impurities

One impurity that can be 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 dimerization⁴ of cyanamide in water. 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. 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.

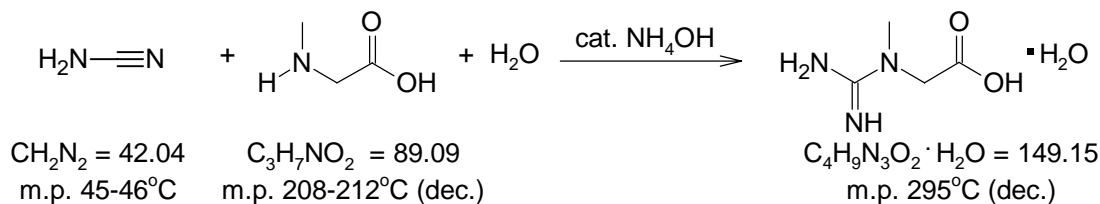
Greening the Chemistry

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 overall mass economy of the reaction, it should greatly reduce the generation of dicyanodiamide. The second is to eliminate use of NaCl. This would also improve the overall mass economy 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

⁴ A dimerization is a reaction linking two of the same type of molecules.

household ammonia (which can be further diluted) would eliminate these safety concerns and the need for a fume hood.

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

- Obtain between 0.40 and 0.44 g of cyanamide. Add to the reaction vessel. (A 10 mL round bottom flask or a 20 mL scintillation vial is recommended, however a beaker will suffice.)
- Obtain between 0.85 and 0.93 g of sarcosine. Add to the reaction vessel.
- Add 2 mL of dilute aqueous ammonia.^{5,6} Add stir bar, cap, and dissolve with stirring.
- Stir for 15 minutes and set aside. (You may also stir 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.

Day # 2 – Isolation of the Product

- Collect the solid by either gravity or vacuum filtration. You may use small portions (~1 mL) of ice-cold DI water to aid the transfer of the solid and to wash the product. 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.
- Weigh your dried product.

Disposal

- 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.⁸

⁵ 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!

⁶ 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.

⁷ This may be disposed of via the drain with copious amounts of water. However, please follow the disposal guidelines for your institution.

⁸ Save your creatine – it makes for an excellent demonstration of the effect of temperature on water solubility.

Assignment: Synthesis of Creatine

1. What is the function of creatine found in the skeletal muscle?

2. Why is creatine so popular among athletes such as power lifters?

3. Is creatine regulated by the Food and Drug Administration?
 - a. Why or why not?

4. To produce creatine the lab use to call for ammonia hydroxide, this causes skin irritation, skin burns and severe irritation to upper respiratory tract. For a GREENER lab we are using household ammonia, why is this safer than ammonia hydroxide?

5. After your mixture was left undisturbed for 24 hours what observations can you make about your flask?