



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

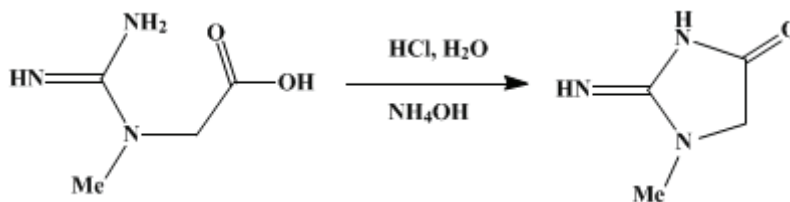
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 1, p.172 (1941); Vol. 4, p.15 (1925).

CREATININE



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1. Procedure

(A) *Creatinine*.—A mixture of 900 g. (6 moles) of commercial *creatine hydrate* (Note 1) with 550 cc. of concentrated *hydrochloric acid* (sp. gr. 1.19) and 150 cc. of water is warmed in a 3-l. flask on the steam bath for twenty-four hours (Note 2). The hot solution is filtered and chilled to 0–5° in an ice bath, and to it is added 1 l. of 28 per cent aqueous *ammonia* (sp. gr. 0.90). The flask is immersed in an ice-salt bath, and the mixture is stirred vigorously until the temperature falls to 0°, when the crystalline *creatinine* is filtered off, washed with ice-cold 28 per cent aqueous *ammonia* (Note 3) until the filtrate is free of chlorides, and finally with ice-cold *methyl alcohol*; the product (Note 4) is then dried to constant weight at 40–50°. The yield (Note 5) is 545–555 g. (80–81 per cent of the theoretical amount).

(B) *Creatinine Zinc Chloride*.—An intimate mixture of 400 g. (2.7 moles) of commercial *creatine hydrate* and 400 g. (2.9 moles) of fused *zinc chloride* is heated in a porcelain dish over a small flame. The mixture melts to a viscous liquid which soon solidifies. The flame is removed when the mixture can no longer be stirred. The mass, when cold, is broken up, and stirred with 500 cc. of cold water until the lumps are softened; the crude *creatinine zinc chloride* is filtered off with suction on a hardened filter paper and washed with ice water to remove excess *zinc chloride*. The crude material is now dissolved in 6 l. of boiling 25 per cent aqueous *acetic acid*, filtered with the use of a little *decolorizing carbon*, and the solution allowed to stand for forty-eight hours. The crystals that have separated are filtered off, washed with ice water, and dried. The weight is 220–230 g. The filtrate and washings are evaporated to 4.5 l. under reduced pressure in a 12-l. flask; 6.5 l. of *methyl alcohol* is added and the mixture allowed to stand in a cool place for twenty-four hours. The crystals that separate are filtered off, washed with cold water and dried, and an additional 150–160 g. is thus obtained. The total yield is 370–380 g. (76–78 per cent of the theoretical amount).

(C) *Creatinine Picrate*.—A mixture of 300 g. (2 moles) of commercial *creatine hydrate* with 190 cc. of concentrated *hydrochloric acid* (sp. gr. 1.19) and 50 cc. of water is warmed in a glass or porcelain dish on a steam bath for twenty-four hours. The resulting mass of *creatinine hydrochloride* crystals is dissolved in 1 l. of water, boiled with a little *decolorizing carbon*, and filtered. The solution is then diluted to 4 l. with distilled water, and heated to boiling in a 12-l. flask under a reflux condenser. To the hot solution is added, with good stirring, a solution of 500 g. (2 moles) of technical *picric acid* (containing 10 per cent of water) in 1250 cc. of warm *methyl alcohol*. Stirring is continued for one hour on the steam bath and the solution allowed to cool. The crystalline precipitate of *creatinine picrate* is filtered off, washed well with cold water, and dried. It forms long needles which melt at 220°; the melting point (Note 6) is unchanged on recrystallization from hot water. The yield is 620–630 g. (89–90 per cent of the theoretical amount).

2. Notes

1. As a rule, the commercial product, which contains one mole of water of crystallization, is entirely satisfactory; but if it is dark in color, it may be recrystallized from water with the use of *decolorizing carbon*.
2. It is suggested that the *hydrochloric acid* solution of *creatine* should be thoroughly decolorized with

Norite before precipitation inasmuch as any color tends to come down with the [creatinine](#). Some of the commercial [creatine](#) contains traces of [iron](#), in which case the addition of 3–4 g. of [tartaric acid](#) before treating with [ammonia](#) will retain the [iron](#) in solution, keeping it from precipitating with and staining the [creatinine](#) (W. W. Hartman, private communication).

3. [Creatinine](#) dissolves readily in pure water but is only slightly soluble in cold concentrated [ammonia](#), while [ammonium chloride](#) is freely soluble.

4. The [creatinine](#) so prepared is practically 100 per cent pure; its recrystallization, while not recommended, may be carried out by dissolving, as rapidly as possible, 1 part by weight in 5 parts of water previously warmed to 65°, and then immediately adding to the warm solution double its volume of [acetone](#), chilling in ice, and filtering after a few hours. The product is finally washed with [acetone](#) and dried. About one-third is lost in the filtrate.

5. The yield could be slightly increased by so modifying the conditions that the total volume of filtrate would be smaller, but this would involve an undue amount of trouble.

6. Special attention was given to the melting-point determination, since two values, 205° and 212–213°, have been recorded in the literature.

3. Discussion

[Creatinine](#) can be prepared from [creatine](#) by the action of mineral acids,¹ by heating in an autoclave² and by treatment with [zinc chloride](#);³ and from [sarcosine](#) and [arginine](#).⁴ The procedure described was developed⁵ since [creatine](#) has become available in relatively large quantities as a by-product.⁶

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 3, 586](#)

References and Notes

1. Liebig, *Ann.* **62**, 298 (1847); Edgar and Wakefield, *J. Am. Chem. Soc.* **45**, 2242 (1923); Edgar, *J. Biol. Chem.* **56**, 3 (1923); Edgar and Hinegardner, *ibid.* **56**, 881 (1923); Greenwald, *ibid.* **81**, 73 (1929); King, *J. Chem. Soc.* 2374 (1930).
2. Folin and Denis, *J. Biol. Chem.* **8**, 399 (1910).
3. Dessaignes, *Jahresber.* 544 (1857); Benedict, *J. Biol. Chem.* **18**, 183 (1914).
4. Bergmann and Zervas, *Z. physiol. Chem.* **173**, 80 (1928); King, *J. Chem. Soc.* 2374 (1930).
5. Edgar, *J. Biol. Chem.* **56**, 3 (1923); Edgar and Hinegardner, *ibid.* **56**, 881 (1923).
6. Edgar, *J. Ind. Eng. Chem.* **14**, 984 (1922).

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

chlorides

[hydrochloric acid](#) (7647-01-0)

[acetic acid](#) (64-19-7)

[ammonia](#) (7664-41-7)

[methyl alcohol](#) (67-56-1)

ammonium chloride (12125-02-9)

iron (7439-89-6)

acetone (67-64-1)

decolorizing carbon,
Norite (7782-42-5)

zinc chloride (7646-85-7)

Creatinine (60-27-5)

creatine hydrate (6020-87-7)

Creatinine Zinc Chloride (62708-52-5)

Creatinine Picrate

creatinine hydrochloride

picric acid (88-89-1)

creatine (57-00-1)

tartaric acid (87-69-4)

sarcosine (107-97-1)

arginine (74-79-3)