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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

*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.*

**dl-METHIONINE**

![Chemical structure](image)

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1. Procedure

(A) *Ethyl Sodium Phthalimidomalonate.*—To a solution of 9.2 g. (0.4 gram atom) of sodium in 300 cc. of absolute alcohol at 60° is added, with efficient stirring, 126 g. (0.41 mole) of ethyl phthalimidomalonate (Org. Syn. Coll. Vol. I, 1941, 271). The mixture is rapidly chilled to 0°; the crystalline product is filtered at once by suction and washed successively with two 200-cc. portions of absolute alcohol and two 200-cc. portions of ether. After first drying in a vacuum desiccator and then heating for eight hours under 15 mm. pressure in a flask suspended in an oil bath at 145–155° (Note 1), the product weighs 108–111 g. (82–85 per cent of the theoretical amount).

(B) *Ethyl 1-Methylthio-3-phthalimidopropane-3,3-dicarboxylate.*—A mixture of 85 g. (0.26 mole) of ethyl sodium phthalimidomalonate and 43 g. (0.39 mole) of β-chloroethyl methyl sulfide (p. 136) is heated in an oil bath at 160–165° in a 1-l. three-necked flask, fitted with a condenser, a thermometer, and a stoppered glass tube for sampling. After one and a half to two hours the mixture is no longer alkaline to litmus. The excess chloroethyl methyl sulfide is distilled under reduced pressure (Note 2), the residual oil is treated with 150 cc. of warm water, and the resulting mixture is transferred to a beaker and chilled. The crystalline material is filtered at once by suction, washed with 100 cc. of cold water, and recrystallized from the smallest possible quantity of warm absolute alcohol. In this way 75–79 g. (76–80 per cent of the theoretical amount) of a pure product, melting at 66–67°, is obtained.

(C) *1-Methylthio-3-phthalamidopropane-3,3-dicarboxylic Acid.*—A solution of 25 g. (0.066 mole) of the above ester in 30 cc. of 95 per cent alcohol is heated on the steam bath in a 200-cc. round-bottomed flask, and 70 cc. of 5N sodium hydroxide is added. The cloudy liquid is heated until a sample gives a clear solution on dilution with water; this occurs after about two hours. The solution is then chilled to 0° and cautiously neutralized to Congo red with 0.2 N hydrochloric acid, whereupon 75 cc. of 5 N hydrochloric acid is slowly added, the temperature being maintained at 0°. The acid separates as
colorless crystals. This separation is completed by the slow addition of 60 cc. of concentrated hydrochloric acid (sp. gr. 1.19). The product is filtered by suction and washed free of salt with small quantities of ice-cold water. After drying in vacuo, the yield is 21.5–22 g. (95.5–98 per cent of the theoretical amount) of a product melting at 141–143°.

(D) Methionine.—A suspension of 21.5 g. (0.063 mole) of this tricarboxylic acid in 350 cc. of hot water is heated on the steam bath, and 40 cc. of concentrated hydrochloric acid (sp. gr. 1.19) is added. Carbon dioxide is immediately evolved, and the substance goes into solution. After heating for one and a half hours, 200 cc. more of concentrated hydrochloric acid is added and heating is continued for forty-five minutes longer. The solution, on cooling, deposits phthalic acid; this is filtered and washed with two 50-cc. portions of water (Note 3). The combined filtrate and washings are evaporated to dryness on the steam bath under reduced pressure, and the dry residue is dissolved in 50 cc. of hot water. The resulting solution is treated with 18 cc. of pyridine and poured into 150 cc. of hot absolute alcohol. Methionine rapidly crystallizes; after cooling it is filtered, washed with alcohol, and dried. The first crop weighs about 6.9 g. The mother liquor is evaporated to dryness; the residue is taken up in 15 cc. of hot water and poured into 50 cc. of absolute alcohol, when a further 1.3 g. is obtained. The total 8.2 g. of nearly pure methionine is suspended in 200 cc. of boiling absolute ether, filtered, and dried. In this way, 7.9–8.0 g. of methionine (84–85 per cent of the theoretical amount), melting at 279–280° (corr.), is obtained.

2. Notes

1. The ethyl sodium phthalimidomalonate crystallizes with 1.5 molecules of alcohol, which is removed only on heating above 140° in vacuo.
2. About 10–12 g. of a pure product can be recovered by redistilling the distillate.
3. The phthalic acid thus recovered melts at 188° and weighs about 7.8 g. (75 per cent of the theoretical amount). Unless most of the phthalic acid is removed at this point, trouble may be encountered by the separation of pyridine phthalate with the methionine.

3. Discussion

The first synthesis of methionine, by the Strecker method, gave a very low yield.1 The procedure given above, based on directions published by the submitters,2 has the advantage over the process of Windus and Marvel3 of giving a much higher yield (54–60 per cent as against 13–19 per cent, based on the β-chloroethyl methyl sulfide consumed).

Methionine has also been prepared, without using β-chloroethyl methyl sulfide, from α-benzoylalmino-γ-butyrolactone4 and from α-acetyl-γ-butyrolactone.5 The first of these syntheses proceeds through ethyl α-benzoylalmino-γ-chlorobutyrate, its reaction product with methyl mercaptan, and hydrolysis of that product. The second synthesis proceeds through α-oximino-γ-butyrolactone which is reduced to α-amino-γ-butyrolactone and converted to 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine. The dihydroxydiketopiperazine is converted to the corresponding dichloroethyl compound, and this, after reaction with methyl mercaptan and subsequent hydrolysis, furnishes methionine.

This preparation is referenced from:


References and Notes

2. Barger and Weichselbaum, ibid. 25, 997 (1931).
Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ester

Ethyl 1-methylthiol-3-phthalimidopropane-3,3-dicarboxylate

tricarboxylic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

erher (60-29-7)

sodium hydroxide (1310-73-2)

carbon dioxide (124-38-9)

pyridine (110-86-1)

sodium (13966-32-0)

Ethyl phthalimidomalonate (5680-61-5)

phthalic acid (88-99-3)

β-Chloroethyl methyl sulfide, chloroethyl methyl sulfide (542-81-4)

methyl mercaptan (74-93-1)

Ethyl Sodium Phthalimidomalonate

Methionine (63-68-3)

pyridine phthalate

α-benzoylamino-γ-butyrolactone

α-acetyl-γ-butyrolactone (517-23-7)

ethyl α-benzoylamino-γ-chlorobutyrate

α-oximino-γ-butyrolactone

α-amino-γ-butyrolactone
dihydroxydiketopiperazine

DL-Methionine (59-51-8)

1-Methylthiol-3-phthalamidopropane-3,3-dicarboxylic Acid

3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine (50975-79-6)