Organic Syntheses

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.

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.

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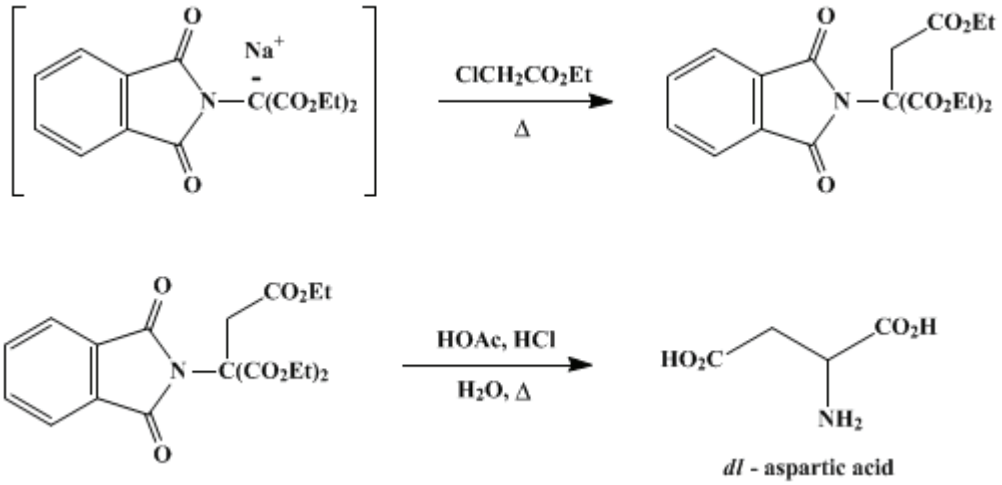
DL-ASPARTIC ACID



Submitted by M. S. Dunn and B. W. Smart[1].
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1. Procedure

A. *Triethyl α-phthalimidoethane-α,α,β-tricarboxylate.* Three hundred and twenty-seven grams (1.0 mole) of diethyl sodium phthalimidomalonate[2] and 735 g. (6.0 moles) of ethyl chloroacetate (b.p. 144–145°) are placed in a 2-l. Claisen flask fitted with a reflux condenser and rubber stoppers. The mixture is heated under reflux in an oil bath at 150–160° for 2.25 hours. The excess ethyl chloroacetate is removed by distillation at 30 mm. until the heating bath temperature reaches 150° and no more distillate is obtained (Note 1). The brown residual mass is cooled and then extracted with 1250 ml. of ether. The oil dissolves, leaving a solid residue which is separated by filtration and washed with 750 ml. of ether. The combined ether extracts are distilled to remove ether, and the residual oil is heated on a steam bath under reduced pressure (35 mm.) to remove traces of ethyl chloroacetate. The yield of triethyl α-phthalimidoethane-α,α,β-tricarboxylate, dried at 45° for 48 hours, is 373–389 g. (95–99%) (Note 2).

B. DL-*Aspartic acid.* A mixture of 383 g. of the above crude product, 1 l. of concentrated hydrochloric acid, 1 l. of glacial acetic acid, and 1 l. of water is boiled under reflux in a 5-l. round-bottomed flask for 2–3 hours. The reflux condenser is then replaced by a fractionating column, and the mixture is slowly distilled until the temperature at the head of the column has risen to 108°. This requires about 13 hours. The distillate amounts to 1.5 l. (Note 3).

The residual mixture is allowed to cool, and the phthalic acid which crystallizes is removed by filtration and washed with 350 ml. of 1% hydrochloric acid (Note 4). The combined filtrate and washings are distilled nearly to dryness on a steam bath under reduced pressure; the bulk of the hydrochloric and acetic acids remaining is removed by slowly adding 300 ml. of water through a dropping funnel while the distillation under reduced pressure is continued. The dark brown residue is warmed on a steam bath with 700 ml. of water, is allowed to cool, and is filtered to remove a small amount of black insoluble matter. The filtrate is decolorized with 2 g. of Norit, 200 ml. of hot water being used to wash the Norit. The volume of the combined filtrate and washings, amounting to about 1.2 l., is measured accurately, and a small portion is analyzed for chloride (Note 5). An amount of pyridine corresponding exactly to the chloride content is added, diluted with 500 ml. of 95% ethanol. The DL-aspartic acid, which crystallizes at once, is separated by filtration after the mixture has stood for 24 hours at room temperature and is washed with 50–100 ml. of cold water (Note 6).

The crude DL-aspartic acid, amounting to 58–60 g., is recrystallized from 600 ml. of hot water and yields 54 g. of pure DL-aspartic acid. The mother liquors on evaporation to about 90 ml. yield an

additional 2–3 g. (Note 7). The total yield of pure colorless DL-aspartic acid is 56–57 g. (42–43%) (Note 8).

2. Notes

1. From 490 to 536 g. of ethyl chloroacetate (b.p. 144–145°) is recovered by the distillation.
2. Although this product cannot be purified by distillation, it contains almost the theoretical amount of nitrogen as shown by Kjeldahl analysis.
3. During the first few hours the distillate contains ethyl acetate; the distillate obtained during the first hour, amounting to 137 ml., distils below 99° and on saturation with sodium chloride yields 115 ml. of crude ethyl acetate.
4. The phthalic acid so obtained is brown and weighs 140–150 g.
5. The total amount of chloride found should be less than 1 mole.
6. The mother liquor contains too little DL-aspartic acid to justify its recovery. When the filtrate and washings are evaporated to a syrup and treated with 500 ml. of 95% ethanol, the pyridine hydrochloride dissolves completely, leaving 8–9 g. of crude glycine which yields little or no sparingly soluble DL-aspartic acid on treatment with a minimum quantity of cold water.
7. The final mother liquor from the recrystallization of DL-aspartic acid yields a small quantity (about 0.5 g.) of glycine.
8. The purity of the recrystallized DL-aspartic acid was established by nitrogen analysis by the Kjeldahl and Van Slyke methods. The decomposition point of this product is 325–348°.

3. Discussion

The above method for the preparation of DL-aspartic acid is a modification of one described by Dunn and Smart.[3] Other methods are: the decomposition of acid ammonium malate by heat;[4] the racemization of active aspartic acid[5] and active asparagine;[6] the reaction of maleic and fumaric acids with ammonia in a closed tube;[7] the reduction of oxalacetic ester oxime;[8] the reduction of silver fumarate by hydroxylamine hydrochloride;[9] the reduction of nitrosuccinic ester;[10] the catalytic reduction and amination of oxalacetic acid;[11] the hydrolysis of triethyl α-aminoethane-α,α,β-tricarboxylate;[12] the hydrolysis of β,β-dicarbethoxy-β-acetylaminopropionic acid;[13] the hydrolysis of dimethyl (carbethoxy) formamidomalonate;[14] the oxidation of β-(2-furyl)-α-alanine by potassium permanganate;[15] and the hydrolysis of diethyl α-acetyl-α-aminosuccinate.[16]

References and Notes

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

maleic and fumaric acids

nitrosuccinic ester

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

ethyl acetate (141-78-6)

ether (60-29-7)

potassium permanganate (7722-64-7)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

Norit (7782-42-5)

pyridine (110-86-1)

Ethyl chloroacetate (105-39-5)

Hydroxylamine hydrochloride (5470-11-1)

Glycine (513-29-1)

phthalic acid (88-99-3)

pyridine hydrochloride (628-13-7)

diethyl sodium phthalimidomalonate

asparagine (70-47-3)

DL-Aspartic acid (617-45-8)

aspartic acid (56-84-8)

silver fumarate

oxalacetic acid (328-42-7)

Triethyl α-phthalimidoethane-α,α,β-tricarboxylate (76758-31-1)

triethyl α-aminoethane-α,α,β-tricarboxylate

β,β-dicarbethoxy-β-acetylaminopropionic acid

dimethyl (carbethoxy)formamidomalonate

β-(2-furyl)-α-alanine

diethyl α-acetyl-α-aminosuccinate