Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

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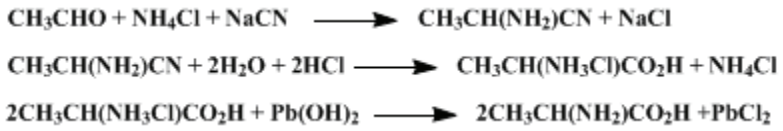
dl-ALANINE



Submitted by E. C. Kendall and B. F. McKenzie.
Checked by C. S. Marvel and W. W. Moyer.

1. Procedure

One hundred and thirty-one grams (3 moles) of freshly distilled acetaldehyde (Note 1) is added to 100 cc. of ether in a 2-l. bottle and cooled to 5° in an ice bath (Note 2). One hundred and eighty grams (3.4 moles) of ammonium chloride dissolved in 550 cc. of water is then added, followed by an ice-cold solution of 150 g. (3.1 moles) of sodium cyanide in 400 cc. of water. The sodium cyanide must be added slowly and with frequent cooling to prevent loss of acetaldehyde by volatilization.

After the sodium cyanide solution is added, the bottle is stoppered securely, placed in a mechanical shaker, and shaken for four hours at room temperature. At the end of this time the solution is transferred to a 3-l. distilling flask and 600 cc. of concentrated hydrochloric acid (sp. gr. 1.19) is added (Hood) (Note 3).

The solution in the flask is distilled over a free flame until separation of salt prevents further heating. It is then transferred to a large evaporating dish, placed on a steam bath and evaporated to dryness (Note 4).

The residue remaining in the dish after evaporation is stirred thoroughly with 800 cc. of 95 per cent alcohol. After filtration the alcohol is distilled on a steam bath and the last traces are removed under vacuum. While still warm the residue is dissolved in 500 cc. of 95 per cent alcohol containing 2 per cent of hydrochloric acid, and cooled. Two hundred cubic centimeters of ether is added, and the solution is filtered. This treatment should remove all but the last traces of sodium chloride and ammonium chloride. The alcohol and ether are removed by distillation and the last of the free hydrochloric acid is removed by distillation under diminished pressure.

The alanine hydrochloride remaining in the flask is dissolved in 1500 cc. of water, and transferred to a metal pail of about 2-l. capacity. Two hundred and twenty grams of yellow lead oxide is added and the mixture is boiled gently for one hour. During the boiling small amounts of water are added at intervals in order to maintain the original volume (Note 5). Upon cooling, the lead chloride crystallizes; it is filtered off and the solution is again boiled one hour with 100 g. of lead oxide. Twenty grams of freshly precipitated lead hydroxide is added slowly and the boiling is continued for ten minutes. Following this the solution is again cooled and filtered (Note 6). The chloride content should now be equivalent to not more than 50–75 cc. of a normal solution (Note 7).

The solution is again brought to a boil and the calculated amount of silver oxide (Note 7) is added to remove the last of the chlorides. The silver chloride is filtered off and the lead is precipitated with hydrogen sulfide. After filtering off the lead sulfide, a light strawcolored solution remains.

The solution is evaporated by boiling to a volume of about 400 cc., and 600 cc. of 95 per cent alcohol is added. When thoroughly cooled, 100–120 g. of alanine is filtered off. This is washed with 200 cc. of alcohol and a pure white product is obtained.

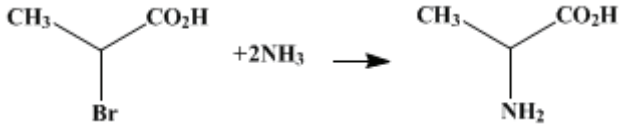
A further crop of 40–50 g. may be obtained by removing the alcohol and water until a volume of about 100 cc. remains, and then adding 250 cc. of alcohol and cooling to 0°. The total yield is 140–160 g. (52–60 per cent of the theoretical amount) (Note 8).

Alanine so prepared is sufficiently pure for most purposes. It may be recrystallized by dissolving in

the least amount of hot water (about 450 cc.) and adding two volumes of alcohol.

2. Notes

1. Acetaldehyde may be conveniently prepared by distilling from paraldehyde in the presence of a trace of sulfuric acid; an efficient fractionating column should be used.
2. A one-half gallon (2-l.) ginger-ale bottle is convenient for this purpose. The necks of these bottles are small and will hold a wire securely.
3. Caution must be observed during the addition of the hydrochloric acid as much hydrogen cyanide is evolved. During the first part of the subsequent distillation it is necessary to prevent fumes from escaping from the receiver into the room.
4. During the evaporation a layer of crystals forms on the surface and must be continually broken. A blast of air blowing over the surface agitates the liquid sufficiently and allows free evaporation.
5. The volume of the solution must be kept large during the treatment with lead oxide as lead chloride will not crystallize from concentrated alanine solutions.
6. If the solution at this point still contains ammonium salts another treatment with 100 g. of lead oxide is necessary.
7. An aliquot portion of the solution is titrated with silver nitrate by the Volhard method. The result of this titration is used in calculating the amount of silver oxide which must be added.
8. A slightly lower yield of alanine may be obtained conveniently from the evaporated alanine hydrochloride by treatment with aniline (Benedict,[1] and G. J. Cox and Harriette King, private communications).



Submitted by Walter C. Tobie and Gilbert B. Ayres.
Checked by John R. Johnson and R. B. Hasbrouck.

1. Procedure

Slowly and with stirring, 100 g. (0.65 mole, 59 cc.) of cold (1–4°) α-bromopropionic acid (Note 1) is added to 3 l. (44.5 moles, 2700 g.) of cold (1–4°) concentrated aqueous ammonia (sp. gr. 0.9) (Note 2) in a 1-gal. glass-stoppered bottle, and the mixture is allowed to stand at room temperature for at least four days (Note 3). The solution is concentrated to a volume of 300 cc. (Note 4), filtered, and concentrated further to 200 cc. The solution is cooled to room temperature and 1 l. of methyl alcohol (Note 5) added. After chilling overnight in a refrigerator (0–4°) the crystals are filtered with suction and washed with 250 cc. each of methyl alcohol and ether (Note 6). The yield is 42–48 g. of crude alanine.

For purification the crude product is dissolved in 200 cc. of water (warming if necessary), 1 l. of methyl alcohol is added, and the mixture chilled overnight. After washing as before, the yield is about 38–42 g. (65–70 per cent of the theoretical amount) of purified *dl*-alanine, m. p. 295° (dec.) on the Maquenne block (Note 7). This product is free of bromide and contains only traces of ammonia. If an especially pure product is desired the material may be reprecipitated from methyl alcohol once more in the same manner (Note 8).

2. Notes

1. α-Bromopropionic acid may be prepared in 80–85 per cent yields by bromination of propionic acid, the general procedure given for α-bromoisovaleric acid (Org. Syn. **20**, 106) being followed and a fraction boiling at 100–102° at 15 mm. being collected. The commercially available α-bromopropionic acid boiling over the same range is also satisfactory.
The use of α-chloropropionic acid gives a poorer yield (43–46 per cent of theoretical) and the product is more difficult to purify owing to the fact that ammonium chloride is less soluble than the bromide in methyl alcohol.

2. The use of a large excess of ammonia (70 moles) minimizes the production of α,α'-iminodipropionic acid and similar by-products.
3. Temperatures above 40° reduce the yield, and chilling after mixing does not increase it. Less than four days' standing gives a reduced yield, but longer standing does not increase the yield.
4. Evaporation may be done in an evaporating dish under a hood, or better by distillation at reduced pressure, using a water pump with a trap. Heating should be gentle at first to avoid violent ebullition. The ammonia may be recovered if desired by absorption in ice water.
5. The grade of technical methyl alcohol known as "Columbian Spirits" may be employed. Ethyl alcohol is much less satisfactory, since it does not dissolve ammonium bromide as well as methyl alcohol does.
6. Filtration is best done with suction on a Büchner funnel. Washing with ether can be omitted without reducing the yield.
7. In a capillary tube the product melts with decomposition at 275–280°, and the melting point varies somewhat with the rate of heating.
8. The last traces of ammonia may be removed by adding 10 g. of permutit when dissolving for the second time, then shaking the mixture thoroughly for three minutes and filtering before the methyl alcohol is added.

3. Discussion

dl-Alanine can be prepared by heating ethyl α-chloropropionate with concentrated aqueous ammonia at 100°;[2] by treatment of α-bromopropionic acid with alcoholic or aqueous ammonia;[3] by the catalytic reduction of a solution of ammonia and ammonium pyruvate,[4] or of the oxime of pyruvic acid;[5] by the action of hydrocyanic acid on aldehyde ammonia;[6] by the action of ammonium cyanide and ammonia on acetaldehyde followed by alkaline hydrolysis;[7] and by methylation of ethyl benzaminomalonate with subsequent hydrolysis and decarboxylation.[8] The procedure described in part A above is based on the modification by Zelinsky and Stadnikov[9] of the hydrocyanic acid and aldehyde ammonia method. A thorough study has been made of the preparation of alanine by the hydrogen cyanide-acetaldehyde method.[10]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 28

References and Notes

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

oxime of pyruvic acid

aldehyde ammonia

ethyl alcohol,
alcohol (64-17-5)

acetaldehyde (75-07-0)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

methyl alcohol (67-56-1)

ether (60-29-7)

ammonium chloride (12125-02-9)

aniline (62-53-3)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

alanine hydrochloride

lead oxide

lead chloride

lead hydroxide

silver oxide (20667-12-3)

silver chloride (7783-90-6)

lead (7439-92-1)

hydrogen sulfide (7783-06-4)

lead sulfide

alanine (56-41-7)

hydrogen cyanide,
hydrocyanic acid (74-90-8)

silver nitrate (7761-88-8)

α-bromopropionic acid (598-72-1)

bromide (24959-67-9)

propionic acid (79-09-4)

α-Bromoisovaleric acid (565-74-2)

α-chloropropionic acid (598-78-7)

α,α'-iminodipropionic acid

ammonium bromide (12124-97-9)

ethyl α-chloropropionate (535-13-7)

ammonium pyruvate

ammonium cyanide

ethyl benzaminomalonate

DL-Alanine (302-72-7)

paraldehyde (123-53-7)