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.

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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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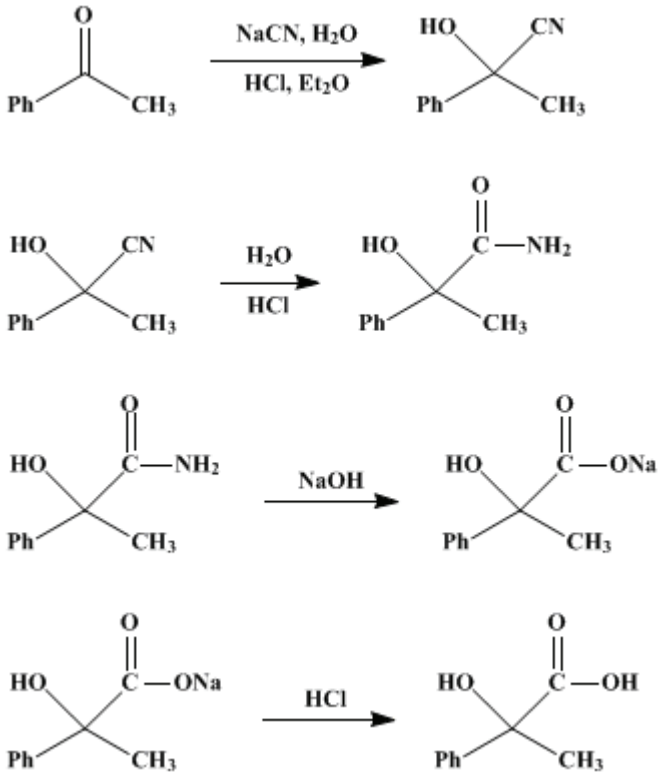
ATROLACTIC ACID



Submitted by Ernest L. Eliel and Jeremiah P. Freeman[1].
Checked by Arthur C. Cope, William F. Gorham, and Roscoe A. Pike.

1. Procedure

Caution! This preparation must be conducted in a hood to avoid exposure to the poisonous hydrogen cyanide that is evolved.

In a 1-l. three-necked round-bottomed flask equipped with a Hershberg stirrer, a thermometer, and a 250-ml. dropping funnel are placed 80 g. (0.67 mole) of acetophenone, 60 ml. of ether, and 100 ml. of water. The apparatus is assembled in a well-ventilated hood, the flask is surrounded by an ice-salt bath, and 82 g. (1.67 moles) of granulated sodium cyanide is added all at once with vigorous stirring. When most of the sodium cyanide has dissolved and the temperature of the mixture has fallen to 5°, 140 ml. (1.7 moles) of concentrated hydrochloric acid is added from the dropping funnel at such a rate that the temperature remains between 5° and 10°. The addition requires about 1.7 hours. After all the acid has been added, the cooling bath is removed and vigorous stirring is continued for 2 hours. The mixture is allowed to settle, and the liquid portion is decanted into a 1-l. separatory funnel. The water layer is returned to the reaction flask, and 100 ml. of water is added to dissolve the salts. The aqueous solution is extracted with four 50-ml. portions of ether, and the original ether layer and extracts are combined in a 500-ml. round-bottomed flask. The ether is distilled at 20–30 mm. pressure (water aspirator) (Note 1), and the residual oil is poured slowly with stirring into 160 ml. of concentrated hydrochloric acid in a 1-l. round-bottomed flask. The mixture then is saturated with hydrogen chloride gas in the hood (Note 2) and (Note 3) and allowed to stand overnight.

Part of the excess hydrogen chloride is removed by blowing (or drawing) air through the solution for 1 hour. The solution then is made alkaline by the slow addition of 50% aqueous sodium hydroxide.

(Note 4) with mechanical stirring and cooling in an ice bath. Solid sodium hydroxide (24 g.) is added, and the mixture is steam-distilled until no more ammonia and acetophenone pass into the distillate (Note 5). About 3–4 l. of distillate is collected (Note 6).

Water is added to the residue if necessary to make the volume 700 ml., and the solution is treated with 2 g. of Norit and filtered with suction (Note 7). The filtrate is extracted with 100 ml. of ether (which is discarded), and acidified by the addition of 80 ml. of concentrated hydrochloric acid. After thorough chilling, preferably overnight in a refrigerator, the precipitated atrolactic acid is collected on a suction filter (Note 8) and air-dried at a temperature not exceeding 65°.

The crude product weighs somewhat more than 70 g. and contains water and sodium chloride. It is dissolved in 500 ml. of boiling benzene, the solution is filtered by gravity, and the solid in the flask and funnel is rinsed with 50 ml. of boiling benzene. The filtrate is concentrated by distillation until no more water collects in the distillate, and the residual solution (300–400 ml.) is cooled. The atrolactic acid which crystallizes is collected on a suction filter and washed with 25 ml. of cold benzene and 25 ml. of commercial pentane (b.p. 30–40°). After air-drying, the cream-colored product amounts to 42.9–43.5 g., m.p. 88–90° with shrinking at 82° (Note 9) and (Note 10). It is pure enough for most purposes but is intermediate in composition between the anhydrous acid and hemihydrate and contains about 3% sodium chloride. This product is dissolved in 200 ml. of boiling water and treated with 10 g. of Norit. The solution is filtered and cooled overnight at 0–5°. The pure, colorless crystals of atrolactic acid hemihydrate that separate are collected on a suction filter and air-dried. The yield is 33.5–34.7 g. (29–30%), m.p. 88–90° with softening beginning at 75°. The anhydrous acid can be obtained by drying the hemihydrate at 55°/1–2 mm.; m.p. 94.5–95°.

2. Notes

1. By maintaining ebullition with a capillary air inlet and cooling the receiver in a bath containing Dry Ice and trichloroethylene, the distillation can be completed in 1 hour or less.
2. The solution becomes homogeneous when it is nearly saturated. An exothermic reaction begins within a few minutes, and some hydrogen chloride gas escapes.
3. The preparation should be carried to this point in 1 day; the time required is about 8 hours. All the operations must be conducted in a well-ventilated hood.
4. About 150 g. of the 50% sodium hydroxide solution is required.
5. The distillation flask should be heated so as to maintain a liquid volume of 600–700 ml.
6. Acetophenone (15–16.5 g., b.p. 92–94°/20 mm.) can be recovered by extracting the distillate with 100 ml. of pentane (b.p. 30–40°). The extract is dried over sodium sulfate, concentrated, and distilled.
7. Only a small amount of solid, in addition to the Norit, should be retained by the filter. If a copious precipitate of sodium atrolactate forms, it should be dissolved by the addition of more water.
8. Only small amounts of crude atrolactic acid are recovered by extracting the filtrate with ether.
9. If the yield is low, the mother liquors should be concentrated to a volume of 50 ml. A second crop of crystals can sometimes be obtained in that way.
10. The submitters have obtained the same yields in preparations on five times this scale.

3. Discussion

Atrolactic acid has been prepared by the oxidation of hydratropic acid with alkaline permanganate,[2] by hydrolysis of α-chloro- or α-bromohydratropic acid,[3,4] by sodium amalgam reduction of β,β-dibromoatrolactic acid,[5] from α-aminohydratropic acid and nitrous acid,[6,7] by permanganate oxidation of 2,5-dihydroxy-2,5-diphenyl-3-hexyne,[8] by reaction of ethyl phenylglyoxylate with methylmagnesium iodide followed by hydrolysis,[9] from pyruvic acid and phenylmagnesium bromide,[10] and from α,α-dibromopropiophenone and sodium hydroxide.[11] The last method could not be adapted to the preparation of the acid in large quantities by the submitters.

The synthesis of atrolactic acid through acetophenone cyanohydrin was first described by Spiegel[12] and has since been used by several other investigators.[6,13,14,15,16,17] The above preparation is adapted from the methods of McKenzie and Clough[15] and Freudenberg, Todd, and Seidler.[17]

References and Notes

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

atrolactic acid hemihydrate

α-chloro- or α-bromohydratropic acid

hydrogen chloride,
hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

sodium hydroxide (1310-73-2)

sodium cyanide (143-33-9)

sodium chloride (7647-14-5)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrous acid (7782-77-6)

Acetophenone (98-86-2)

Norit (7782-42-5)

sodium (13966-32-0)

Phenylmagnesium bromide (100-58-3)

methylmagnesium iodide (917-64-6)

ethyl phenylglyoxylate (1603-79-8)

Pentane (109-66-0)

Pyruvic acid (127-17-3)

acetophenone cyanohydrin

Atrolactic acid (515-30-0)

sodium atrolactate

hydratropic acid (492-37-5)

β,β-dibromoatrolactic acid

α-aminohydratropic acid (6945-32-0)

2,5-dihydroxy-2,5-diphenyl-3-hexyne

α,α-dibromopropiophenone