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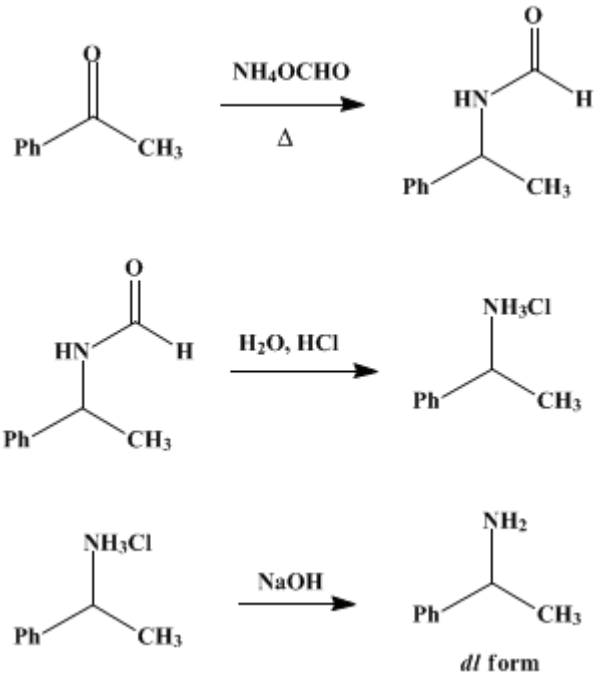
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.017.0076

Organic Syntheses, Coll. Vol. 2, p.503 (1943); Vol. 17, p.76 (1937).

α-PHENYLETHYLAMINE

[Benzylamine, α-methyl-]



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1. Procedure

In a 500-cc. modified Claisen flask are placed 250 g. (4 moles) of ammonium formate (Note 1), 150 g. (1.25 moles) of acetophenone (Note 2), and a few chips of porous plate. The flask is fitted with a cork carrying a thermometer extending nearly to the bottom, and the side arm is connected to a small condenser set for distillation. On heating the flask with a small flame the mixture first melts to two layers and distillation occurs; at 150–155° it becomes homogeneous and reaction takes place with moderate foaming. The heating is continued, more slowly if necessary, until the temperature reaches 185°. During this process water, acetophenone, and ammonium carbonate distil; about three hours is required and little attention is necessary. At 185° the heating is stopped and the upper layer of acetophenone is separated from the distillate and returned, without drying, to the reaction flask. The mixture is then heated for three hours at 180–185°. The distillate is extracted with 25–30 cc. of benzene to recover acetophenone (Note 3), and the aqueous portion is discarded.

The reaction mixture is cooled and then shaken in a 500-cc. separatory funnel with 150–200 cc. of water to remove ammonium formate and formamide. The crude α-phenylethylformamide is drawn off into the original flask, and the water layer is extracted with two 30-cc. portions of benzene and discarded. The benzene extracts are united with the main portion, and 150 cc. of concentrated hydrochloric acid is added, together with a few pieces of porous plate. The mixture is cautiously heated until the benzene has distilled and then boiled gently for forty to fifty minutes longer. Hydrolysis proceeds rapidly, and the mixture becomes homogeneous except for a small layer of acetophenone and other neutral substances. The mixture is cooled and extracted first with 50 cc. of benzene and then with three or four 25-cc. portions of the solvent. The extracts are saved for the recovery of acetophenone (Note 3).

The aqueous acid solution is transferred to a 1-l. round-bottomed flask provided with a separatory

funnel and equipped for steam distillation. A solution of 125 g. of sodium hydroxide in 250 cc. of water is added through the funnel, and the mixture is distilled with steam (Note 4). The first liter of distillate contains most of the amine, but the distillate should be collected until it is only faintly alkaline. A small residue containing di-(α-phenylethyl)-amine and neutral substances remains in the flask and may be discarded.

The distillate is extracted with five 50-cc. portions of benzene, and the benzene solution is dried thoroughly with powdered sodium hydroxide and distilled (Note 5). Most of the amine distils at 184–186°, but the fraction distilling at 180–190° is sufficiently pure for most purposes (Note 6). The yield of this fraction is 80–88 g. By combining the benzene fore-run with the distillation residue, extracting with dilute acid, and recovering the amine as above, an additional 10–12 g. of material can be obtained (Note 7), making the total yield 90–100 g. (60–66 per cent of the theoretical amount based on the acetophenone taken) (Note 8).

2. Notes

1. Ammonium formate may be made in quantity by treating solid ammonium carbonate with a slight excess of commercial 85 per cent formic acid and concentrating the solution, in stages, on a steam bath under reduced pressure. The slightly moist product obtained by suction filtration is suitable for this preparation.
2. Eastman's "practical" acetophenone, m.p. 16–20°, was used. Directions for preparing acetophenone are given in Org. Syn. Coll. Vol. I, **1941**, 111.
3. The benzene solution is washed with dilute alkali, dried, and distilled, the fraction boiling at 198–207° being collected.
4. In the steam distillation it is advisable to heat the distillation flask directly so that the volume remains nearly constant.
5. The amine attacks cork and rubber and absorbs carbon dioxide from the air. It is best distilled in a flask having an in-set side arm and collected in a distilling flask protected by a soda-lime tube.
6. If very pure amine is desired the product described above is dissolved with 1.04 parts of crystalline oxalic acid in 8 parts of hot water. After clarification with Norite, the filtered solution on cooling deposits crystals of the acid oxalate. About 5 g. of the salt remains in each 100 cc. of the mother liquor; most of this can be obtained by evaporation and further crystallization. The amine is liberated from the pure oxalate with potassium hydroxide, distilled with steam, and purified as described above. When a known amount of amine is desired in water solution (as for optical resolution), a weighed amount of the (anhydrous) oxalate is decomposed and the amine is distilled quantitatively with steam.
7. When several runs are to be made the acid solution of the amine may be combined with the next run previous to steam distillation.
8. The method described is rather general. With appropriate modifications for the purification of the amine the method yields α-*p*-tolylethylamine (72 per cent), α-*p*-chlorophenylethylamine (65 per cent), α-*p*-bromophenylethylamine (63 per cent), α-*p*-xenylethylamine (66 per cent), and α-(β-naphthyl)-ethylamine (84 per cent) from the corresponding ketones.

3. Discussion

The present procedure was developed from those of Wallach[1] and Freylon,[2] based upon the general method discovered by Leuckart.[3] α-Phenylethylamine also can be prepared satisfactorily by the reduction of acetophenone oxime with sodium and absolute alcohol[4] or sodium amalgam,[5] or with ammonium amalgam,[6] or electrolytically.[7] The amine has been obtained by reducing acetophenone phenylhydrazone with sodium amalgam and acetic acid;[8] from α-phenylethyl bromide and hexamethylenetetramine;[9] by the action of methylmagnesium iodide on hydrobenzamide;[10] and by reducing acetophenone in the presence of ammonia with hydrogen and a nickel catalyst,[11] a method for which detailed directions are given in Volume 23 of this series.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 2, 506
- Org. Syn. Coll. Vol. 3, 717

- Org. Syn. Coll. Vol. 5, 909

References and Notes

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

α-p-Xenylethylamine

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonium carbonate (506-87-6)

ammonia (7664-41-7)

Benzene (71-43-2)

formamide (75-12-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

formic acid (64-18-6)

Oxalic acid (144-62-7)

carbon dioxide (124-38-9)

nickel (7440-02-0)

Acetophenone (98-86-2)

Norite (7782-42-5)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

oxalate

methylmagnesium iodide (917-64-6)

hexamethylenetetramine (100-97-0)

Ammonium (14798-03-9)

α-Phenylethylamine,
Benzylamine, α-methyl- (3886-69-9)

ammonium formate (540-69-2)

α-phenylethylformamide (6948-01-2)

di-(α-phenylethyl)-amine

α-(β-naphthyl)-ethylamine

acetophenone oxime

acetophenone phenylhydrazone

α-phenylethyl bromide (585-71-7)

hydrobenzamide

α-p-Tolylethylamine

α-p-Chlorophenylethylamine (6299-02-1)

α-p-Bromophenylethylamine (24358-62-1)

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