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.

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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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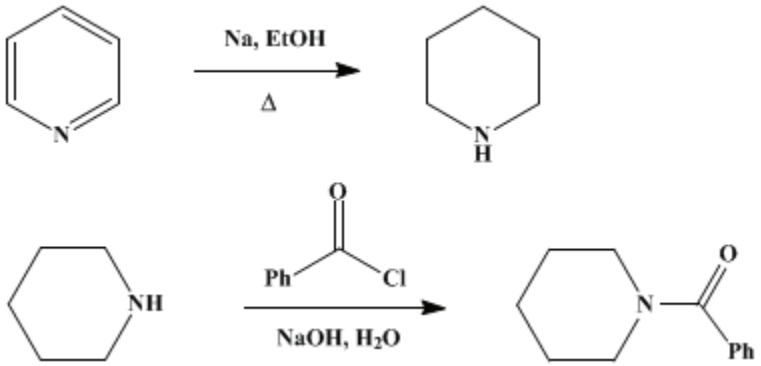
Organic Syntheses, Coll. Vol. 1, p.99 (1941); Vol. 9, p.16 (1929).

BENZOYL PIPERIDINE

[Piperidine, 1-benzoyl-]



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1. Procedure

In a 5-l., two-necked, round-bottomed flask, fitted with an efficient reflux condenser (Note 1), is placed a mixture of 130 g. (131 cc., 1.64 moles) of dry pyridine (Note 2) and 3 l. of absolute alcohol (see Note 2 on p. 249). During the course of forty to fifty minutes 450 g. (19.6 atoms) of sodium is added gradually. The sodium is added in as large pieces as can be inserted through the second opening in the flask. One and one-half liters of absolute alcohol is now added and the mixture heated over an oil bath for two to three hours until the sodium disappears. It is desirable not to allow the reaction mixture to cool (Note 3) at this point but to separate the piperidine immediately. The condenser is set for distillation and a separatory funnel is inserted through the stopper in the second opening of the flask. The alcohol is then distilled using an oil bath (Note 4). The addition of a piece of zinc facilitates an even distillation. During this procedure, water to the amount of 1700–1800 cc. is added to the reaction mixture through the separatory funnel, slowly at first and later as rapidly as possible. At the beginning, this addition must be very cautious as the heat evolved causes a very distillation of alcohol. After about 200 cc. of water has been added, the mixture begins to solidify and remains semi-solid until most of the water has been added. The distillation is continued until practically all the alcohol has distilled (three to four hours). At the end of this time there remains in the distilling flask about 1500 cc. of residue, which is discarded. The distillate is about 5 l. in volume. To this is added 200 cc. of concentrated hydrochloric acid (sp. gr. 1.19) and the mixture is then returned to the distilling flask. The alcohol is removed by distillation on a steam bath until the residual volume in the flask amounts to about 600–800 cc.; this requires two to three hours.

The residue is then transferred to a 2-l. round-bottomed flask fitted with a mechanical stirrer and separatory funnel. The mixture is treated with stirring with a solution of 186 g. of technical sodium hydroxide or 170 g. (4.25 moles) of c.p. sodium hydroxide in about 300 cc. of water. With continuous stirring 235 g. (1.67 moles) of benzoyl chloride is now added during the course of one hour, keeping the temperature down by cooling with running water. After the addition, the reaction mixture is cooled, the amide separated (Note 5), washed with a little water (Note 6) and distilled (Note 7) under reduced pressure. The product boils at 180–184° /20 mm., 191–194° /27 mm., 240–244° /130 mm., and weighs 240–250 g. (77–81 per cent of the theoretical amount).

Benzoyl piperidine thus obtained is a straw-colored viscous liquid. Upon long standing or seeding with crystalline benzoyl piperidine, the compound crystallizes in long, colorless needles which melt at 44°. The literature reports 48° as the melting point of the pure material.

Using 180 g. of pyridine in place of the 130 g. suggested, and a corresponding increase in the other

chemicals except the sodium and alcohol, a yield of 300–326 g. of benzoyl piperidine is obtained. This is a smaller percentage yield (70–75 per cent of the theoretical amount) but the actual yield more than repays for the excess of pyridine used (Note 8).

2. Notes

1. A reflux condenser 180 cm. long with inner tube 2 cm. in diameter is recommended. If a smaller condenser is employed, the reaction cannot be run as rapidly as is desirable to give the best results. If the reaction is not run rapidly sodium ethoxide separates in the flask.
2. Unless the purity of the pyridine is known, it should be dried with solid sodium hydroxide and distilled before use. For this work a fraction boiling at 112–117° was used.
3. If the alcohol solution is allowed to cool before the addition of the water, it solidifies and is remelted only with difficulty. If it is desired to suspend the process, the water should be added first and then the solution will not solidify.
4. In distilling the piperidine from the strong alkaline solution, the flask must be suspended in the oil bath. Direct heating raises the temperature of the flask to such a point that the alkali rapidly etches through it.
5. A troublesome emulsion sometimes results after benzoylation. This usually may be broken up by the addition of more strong sodium hydroxide solution. In case an emulsion is formed which cannot be broken it is possible to extract the product with benzene.
6. Any sodium hydroxide carried into the distilling flask causes decomposition of the benzoyl piperidine during distillation and consequently a considerably lower yield results. For this reason it is well to wash the product carefully in the separatory funnel with a little water after the alkaline solution has been drawn off.
7. Benzoyl piperidine is much given to superheating, making distillation difficult.
8. If piperidine is available, benzoyl piperidine for use in the preparation of pentamethylene bromide (p. 428) may be prepared by direct benzoylation. A mixture of 105 g. of sodium hydroxide (2.6 moles), 170 g. of piperidine (2.0 moles) (b.p. 104–109°), and 800 cc. of water is treated with 280 g. (2 moles) of benzoyl chloride using the apparatus and procedure described above; the temperature is kept at 35–40°. The oily product is separated after dilution with 250 cc. of benzene if necessary (Note 5), dried with a small quantity of potassium carbonate and distilled. The portion boiling at 172–174° /12 mm. weighs 330–345 g. (87–91 per cent of the theoretical amount). The first few cubic centimeters of the distillate may be colored by a reddish impurity, in which case a forerun is collected separately.

3. Discussion

Benzoyl piperidine can be prepared by the action of benzoyl chloride on piperidine in the presence of alkalies.[1]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 1, 428
- Org. Syn. Coll. Vol. 3, 432
- Org. Syn. Coll. Vol. 8, 326

References and Notes

1. Cahours, Ann. chim. phys. (3) **38**, 87 (1853); Schotten, Ber. **17**, 2545 (1884); **21**, 2238 (1888).

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

alcohol (64-17-5)

potassium carbonate (584-08-7)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

sodium hydroxide (1310-73-2)

benzoyl chloride (98-88-4)

pyridine (110-86-1)

zinc (7440-66-6)

sodium (13966-32-0)

BENZOYL PIPERIDINE,
Piperidine, 1-benzoyl- (776-75-0)

piperidine (110-89-4)

sodium ethoxide (141-52-6)

pentamethylene bromide (111-24-0)