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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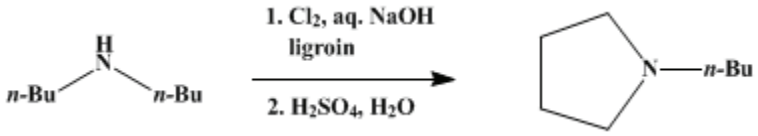
1-*n*-BUTYLPYRROLIDINE

[Pyrrolidine, 1-butyl-]



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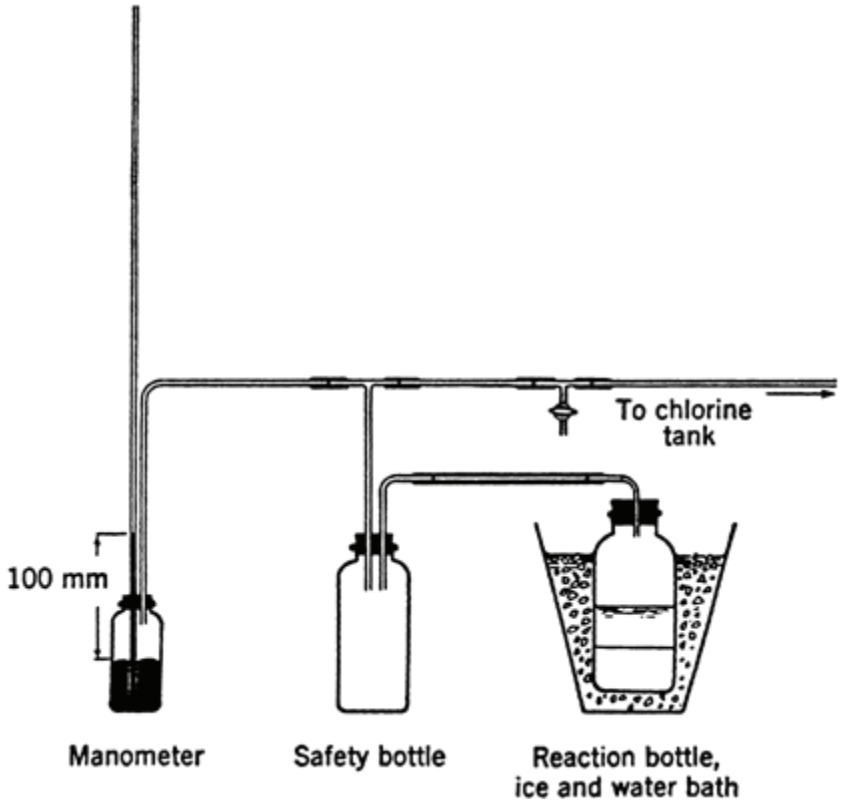
1. Procedure

This preparation must be carried through the ring closure without interruption.

The apparatus is arranged as in Fig. 7. In a bottle of about 1.5-l. capacity are placed 64.5 g. (0.5 mole) of di-*n*-butylamine,[1] 350 ml. of ligroin (Note 1), and 350 ml. of 3 *N* sodium hydroxide (Note 2). The bottle is fitted with an inlet tube which passes only 1 in. through the stopper. The mixture is cooled in an ice bath (Note 3), and chlorine from a cylinder is passed in under pressure (Note 4). The bottle is kept in the ice bath and is shaken during the addition to aid in absorption of the gas. The rate of shaking and the valve on the chlorine cylinder are so regulated that the pressure as indicated on the manometer is maintained between 100 and 150 mm. (Note 5). The addition of the chlorine is continued until the white fumes of the hydrochloride, which form when chlorine comes in contact with the amine vapor, disappear, and the non-aqueous layer takes on a greenish yellow color, due to a slight excess of chlorine. This indicates that chlorination is complete (Note 6).

Fig. 7.



The ligroin solution of the chloramine is separated from the aqueous layer in a chilled, short-stemmed 1-l. separatory funnel and washed successively with 50 ml. of ice-cold 3 *N* sodium hydroxide (Note 7), 50 ml. of ice water, and 50 ml. of cold 2 *N* sulfuric acid. The ligroin solution becomes nearly colorless. The chloramine is extracted from the solution with sulfuric acid in the following manner. An ice-cold mixture of 200 ml. of concentrated sulfuric acid (sp. gr. 1.84) and 80 ml. of water is allowed to stand in contact with the ligroin solution for 10 minutes *without* shaking, then for 20 minutes *with* occasional shaking; the mixture is kept cool by immersion in an ice bath. After separation from the acid layer, the ligroin is extracted with two 60-ml. portions of cold concentrated sulfuric acid. The combined sulfuric acid extracts are used for ring closure (Note 8). The ligroin, which contains not more than a trace of chloramine, is discarded.

A 1-l. wide-mouthed Erlenmeyer flask, fitted with a propeller-type stirrer and a thermometer, is set in an oil bath. A mixture of 40 ml. of concentrated sulfuric acid and 10 ml. of water is placed in the flask, the oil bath is heated to 120°, and the cold sulfuric acid solution of the chloramine is allowed to flow into the heated acid from the short-stemmed separatory funnel (Note 9). The addition, which requires 30–40 minutes (Note 10), is carried out at such a rate that the temperature of the reaction mixture in the flask is dropped from 120° rapidly to 95° by the addition of the cold chloramine solution, and thereafter at such a rate that the temperature of the reaction mixture remains at 90–100°, preferably at 95°. The reaction is exothermic, and the rise in temperature is controlled by the addition of the cold chloramine solution. To avoid an undue rise in temperature after the last addition of the chloramine, the oil bath is removed, and the flask and contents are allowed to come to room temperature.

A 5-l. flask is fitted with a separatory funnel and arranged for steam distillation (p. 64). Two liters of crushed ice is placed in the flask, and the sulfuric acid solution, cooled to 0°, is slowly added. The amines are then liberated (Note 11) by adding cold concentrated sodium hydroxide solution (650 g. in 1.5 l. of water) through the separatory funnel. The amines are steam-distilled and collected in a solution of 100 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 200 ml. of water (Note 12). Distillation is continued until all amine has passed over, as indicated by a negative test with litmus paper. About 2 l. of distillate is usually required.

The amine hydrochloride solution is evaporated nearly to dryness on a steam bath (Note 13) and transferred with about 300 ml. of water to a 1-l. three-necked flask equipped with a stirrer,[2] separatory funnel, and condenser. The stirrer is started, and the acid solution is cooled to 0° by immersing the flask in an ice bath. The amines are liberated by adding slowly 100 g. of sodium hydroxide dissolved in 250 ml. of water.

Hinsberg separation. To this solution, which should be cold (5–8°), is now added 23 g. of benzenesulfonyl chloride,[3] and the mixture is stirred vigorously for 30 minutes. The separatory funnel is replaced by a stopper bearing a thermometer, and the contents of the flask are warmed to 40° and stirred until the odor of the acid chloride is no longer noticeable. This usually requires about 30 minutes. The 1-*n*-butylpyrrolidine is separated (Note 14) from the non-volatile di-*n*-butylbenzenesulfonamide by steam distillation, the amine being collected in dilute acid (Note 12) as before. The acid solution is then evaporated to dryness, and the amine is liberated by adding 20% sodium hydroxide solution until the aqueous layer turns red litmus blue. The amine is extracted by one 200-ml. portion of ether, and the ethereal solution is dried over 15–20 pellets of potassium hydroxide. After the ether has been distilled from the decanted solution, the residue is distilled from an oil bath. The yield of 1-*n*-butylpyrrolidine boiling at 154–155°/758 mm. is 44–51 g. (70–80%); n_D^{27} 1.437 (Note 15).

2. Notes

1. Any fraction boiling within the range 60–90° may be used.
2. This is obtained by dissolving 42 g. of sodium hydroxide in 350 ml. of water.
3. All equipment, the solutions, and the chloramine solution should be kept ice-cold to prevent decomposition during the preparation. Apparatus may be stored in a refrigerator.
4. As the addition of chlorine is started, the stopper in the reaction bottle is loosened momentarily and the chlorine is allowed to replace most of the air in the system.
5. As the chlorine passes initially into the bottle, the pressure rises rapidly. Shaking greatly increases the rate of absorption, and the pressure drops. The chlorine valve is then regulated so as to maintain the

proper pressure with shaking. One hundred millimeters was selected as the approximate pressure, since the rate of chlorination under this pressure is satisfactory.
6. A large excess of chlorine is undesirable and may result in greatly decreased yields. The time required varies widely, being dependent upon the chlorine pressure maintained and the vigor of the shaking. The checkers found that 20 minutes was ample under their conditions; the submitters reported that 1–1.5 hours was required.
7. If the green color, due to excess chlorine, is not removed by one washing, the operation is repeated as many times as may be necessary.
8. The sulfuric acid layers are transferred directly into the 500-ml. short-stemmed separatory funnel to be used in the next step. The solution, which usually has a light brown color, should be cold and well mixed before the ring-closure operation. The ratio of acid to water is important, and only the amounts specified should be used.
9. The funnel and contents may be supported over the reaction flask during the addition without cooling.
10. The rate of addition should be as rapid as possible provided that the proper temperature is maintained. Deviation of more than 5° from the optimum reaction temperature of 95° results in reduced yields.
11. This reaction is vigorous, and the solution of alkali should be added slowly while the flask is shaken gently with a rotary motion.
12. An adapter (rubber connector and glass tube) from the lower end of the condenser should extend below the surface of the absorbing acid in the receiver. To reduce fuming, a 3- to 4-mm. layer of ligroin is placed over the acid solution. The acid solution may be stirred occasionally.
13. Use of reduced pressure considerably diminishes the time required.
14. The amine can be separated from the sulfonamide by extracting both with ether, drying this extract over solid potassium hydroxide, and fractionating. The pyrrolidine distils smoothly, but the yield is slightly lower.
15. Several other pyrrolidines of this series can be prepared by the same general method. The temperature required for ring closure and the percentage yield of pyrrolidine vary with the different amines used. The tabulated temperatures are given as approximately correct for the ring closure of the N-chloro-derivatives of the amines listed. With lower-boiling pyrrolidines, incomplete separation from the ether may result in lower yields.

Amine	*Optimum Temperature, °C*	*Pyrrolidine Formed*
Methyl-*n*-butyl	100–110	1-Methylpyrrolidine
Ethyl-*n*-butyl	110–115	1-Ethylpyrrolidine
n-Propyl-*n*-butyl	80–85	1-*n*-Propylpyrrolidine
Methyl-*n*-amyl	90–100	1,2-Dimethylpyrrolidine
Ethyl-*n*-amyl	80–90	1-Ethyl-2-methylpyrrolidine
Methyl-*n*-octyl	60–70	1-Methyl-2-*n*-butylpyrrolidine

3. Discussion

1-*n*-Butylpyrrolidine has been prepared by heating the corresponding N-bromoamine in concentrated sulfuric acid;[4] by catalytic reduction of N-butylpyrrole;[5] from furan and *n*-butylamine in the presence of aluminum oxide at 350–450°;[6] from 1,4-dichlorobutane and *n*-butylamine with potassium carbonate.[7] The procedure described is adapted from a preparation reported earlier.[8]

References and Notes

1. *Org. Syntheses* Coll. Vol. **1**, 202 (1941).
2. *Org. Syntheses* Coll. Vol. **1**, 33, Fig. 2*B* (1941).
3. *Org. Syntheses* Coll. Vol. **1**, 84 (1941).
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5. Ochiai, Tsude, and Yokoyama, *Ber.*, **68**, 2293 (1935).

6. Yurev, Tronova, L'vova, and Bukshpan, *J. Gen. Chem. U.S.S.R.*, **11**, 1128 (1941).
7. Elderfield and Hageman, *J. Org. Chem.*, **14**, 605 (1949).
8. Coleman and Goheen, *J. Am. Chem. Soc.*, **60**, 730 (1938).

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

ligroin

potassium carbonate (584-08-7)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

Benzenesulfonyl chloride (98-09-9)

chlorine (7782-50-5)

potassium hydroxide (1310-58-3)

Furan (110-00-9)

n-Propyl-n-butylamine (20193-21-9)

n-butylamine (109-73-9)

aluminum oxide (1344-28-1)

1,4-dichlorobutane (110-56-5)

Pyrrolidine, 1-butyl-,
1-n-BUTYLPYRROLIDINE (767-10-2)

pyrrolidine (123-75-1)

1-Methylpyrrolidine (120-94-5)

1-Ethylpyrrolidine (7335-06-0)

1,2-Dimethylpyrrolidine

1-Ethyl-2-methylpyrrolidine

N-bromoamine

N-butylpyrrole (589-33-3)

di-n-butylamine (111-92-2)

Methyl-n-butylamine (110-68-9)

Methyl-n-amylamine (25419-06-1)

Ethyl-n-butylamine (13360-63-9)

Ethyl-n-amylamine

di-n-butylbenzenesulfonamide (5339-59-3)

1-n-Propylpyrrolidine

1-Methyl-2-n-butylpyrrolidine

di-n-butylchloramine

Methyl-n-octylamine