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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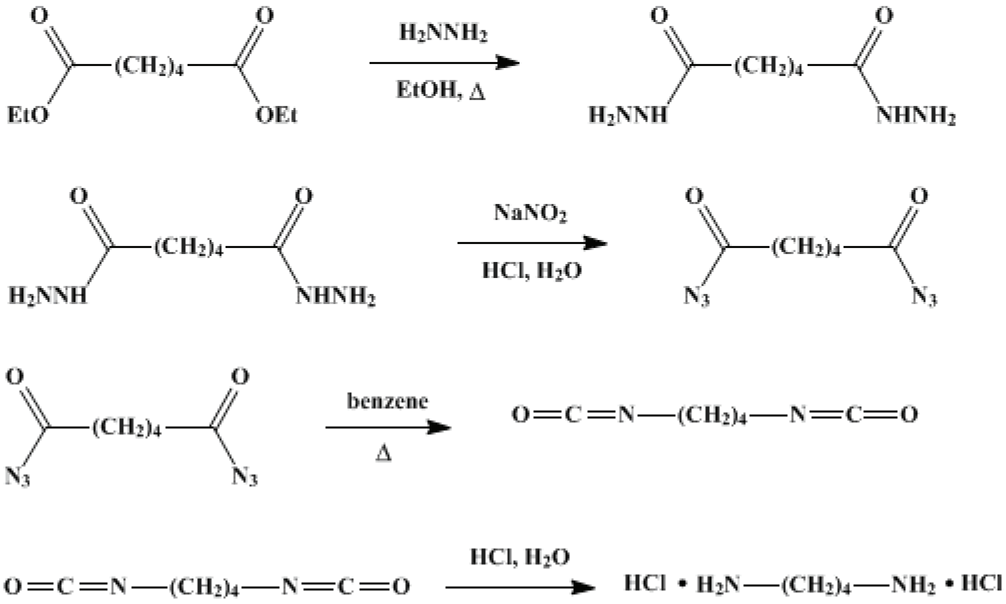
PUTRESCINE DIHYDROCHLORIDE

[1,4-Butanediamine dihydrochloride]



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1. Procedure

A. *Adipyl hydrazide.* A solution of 120 ml. of 85% aqueous hydrazine hydrate (105 g., 2.0 moles) (Note 1) and 25 ml. of absolute ethanol is brought to a gentle boil in a 500-ml. three-necked flask provided by means of ground glass joints with a ball joint-sealed mechanical stirrer (Note 2), a reflux condenser, and a dropping funnel. One hundred and one grams (0.5 mole) of diethyl adipate[2] is added dropwise to the boiling stirred solution at such a rate that a separate liquid phase does not accumulate in the reaction mixture (Note 3). This operation requires 1–2 hours, at the end of which time the contents of the flask will have largely crystallized. The boiling is continued for 5 minutes after the completion of the addition, and the contents of the flask are then cooled to room temperature with running water. The crystals are washed onto a Büchner funnel with the aid of about 100 ml. of absolute ethanol used in several portions. The precipitate is dried by suction, and the product is washed once with 25 ml. of ether. After drying in air (or at 100°) the adipyl hydrazide weighs 77–80 g. (88–92%) and is of good quality, with a melting point about 170° (Note 4). Concentration of the filtrate to a volume of about 25 ml. in an air stream on a steam bath yields an additional 2.5 g. of nearly pure material; total yield 91–95%.

B. *Putrescine dihydrochloride.* A 2-l. wide-mouthed Erlenmeyer flask containing 200 ml. of concentrated hydrochloric acid and 400 g. of cracked ice is clamped in an ice-salt bath and provided with an efficient stirrer (inefficient stirring may lower the yield). The stirring is started, and 80 g. (0.46 mole) of adipyl hydrazide is added all at once, followed by 500 ml. of ether (Note 5). While the temperature is maintained below 10° (Note 6), a solution of 80 g. (1.15 moles) of sodium nitrite in 150 ml. of water is added over about 30 minutes through a dropping funnel whose stem reaches below the bottom of the ether layer, but not into the path of the stirrer. *The operations in the next paragraph should be conducted without delay after the completion of the addition of the nitrite.*

The cold reaction mixture, which may be freed from suspended solid by rapid filtration through a cotton plug, is transferred to a 2-l. or 3-l. separatory funnel, and the aqueous layer is drawn off into the original reaction flask. The ether layer is poured into a 2-l. Erlenmeyer flask containing about 50 g. of anhydrous calcium chloride, and this flask is placed in the ice bath in which the diazotization was run. The cold aqueous layer is then extracted with two 100-ml. portions of chilled ether, which are combined with the first ether extract. After 5 minutes with occasional swirling, the ether solution of adipyl azide (Note 7) is sufficiently dry, and it is poured into a 2-l. round-bottomed flask containing 350–400 ml. of benzene (Note 8). The calcium chloride is rinsed with a 50-ml. portion of ether, which is added to the same flask.

The ether is distilled gently from a steam bath, preferably through a short fractionating column; nitrogen will be evolved at the same time. When the volume of the contents of the flask has reached about 400 ml., the flask is heated strongly on the steam bath for about 15 minutes to complete the decomposition of the azide (Note 9). The flask is removed from the steam bath, and 200 ml. of concentrated hydrochloric acid is added cautiously to the hot solution (Note 10). The flask is allowed to stand with occasional swirling until the carbon dioxide evolution has ceased (about 15 minutes). The mixture is heated strongly on a steam bath for about 15 minutes more, and the solvents are then distilled from a steam bath under aspirator vacuum (Note 11). When the contents of the flask have become a crystalline paste, the vacuum is temporarily disconnected, and the inner walls of the flask are washed down with about 50 ml. of ethanol. The vacuum is renewed cautiously, and the mixture is distilled to dryness (Note 12).

The residue of crystalline putrescine dihydrochloride is rinsed onto a Büchner funnel with the aid of 100–200 ml. of absolute ethanol used in several portions. The last portions of ethanol are used as wash liquid for the crystals. The crystals are finally pressed dry and washed with 25 ml. of ether. The air-dried product weighs 53–55 g. (72–74%) and melts above 275°. Analysis for chlorine indicates that the salt is anhydrous. Concentration of the filtrate to a volume of about 25 ml. yields an additional 1–2 g.; total yield 73–77%. The entire synthesis may be completed in one day.

2. Notes

1. Eastman Kodak Company practical grade was used.
2. Mechanical stirring is not strictly necessary; however, severe bumping is sometimes encountered if it is not used. Hydrazine attacks both cork and rubber. If a dropping funnel with ground glass joint is not available, an ordinary dropping funnel may be placed at the top of the reflux condenser.
3. If unreacted ester is allowed to accumulate, some secondary hydrazide may be formed, with consequent loss of yield in the next step.
4. The melting point of adipyl hydrazide reported in the literature[3] is 171°; however, values as high as 179° have been observed. The checkers observed values of 174–177° and 179–181° for products of two runs, when the crystals were placed on a hot stage after the temperature had reached 160°.
5. Ethanol-free ether should be used. Dropwise addition of 50 ml. of concentrated sulfuric acid to 1 l. of ether, and distillation of the ether from a steam bath gives a satisfactory solvent.
6. To maintain this temperature at the rate of addition of the nitrite indicated will probably require the occasional addition of cracked ice to the reaction mixture. Only occasional checking of the temperature is necessary. If the temperature is kept below 0°, slightly better yields are obtained. The addition of Dry Ice directly to the ether layer accomplishes this easily. Temperatures above 10° cause a loss in yield, but apparently create no hazard.
7. Ethereal solutions of adipyl azide are quite safe, but the free azide is somewhat explosive and should not be isolated. If storage of an intermediate is desired, the azide should be converted to the urethane by the procedure given below. The urethane is quite stable to storage; also, the procedure *via* the urethane gives improved yields in some amine syntheses.

The dried ethereal solution of adipyl azide is added to a 2-l. flask containing 400 ml. of absolute ethanol, and the ether and some of the ethanol are distilled on a steam bath through a short fractionating column. When the volume has reached about 200 ml., the solution may be poured into a 500-ml. Erlenmeyer flask, and the remainder of the solvents removed on a steam bath by means of an air stream. The residual, waxy, crystalline cake of N,N'-dicarbethoxyputrescine weighs 84–91 g. (79–85%) and melts at 76–81°. It may be kept indefinitely.

If the urethane is to be hydrolyzed immediately, there is no need to isolate it. Instead, after distillation of most of the ether and alcohol from the flask in which the urethane is formed, 700 ml. of concentrated hydrochloric acid is added, and the mixture is heated under reflux for 4 hours. The solution is then distilled from a steam bath under aspirator vacuum (Note 11), and the putrescine dihydrochloride is isolated as described above. The total yield is 55–57 g. (74–77%).

The isolated urethane may be hydrolyzed by this procedure at any time. For the hydrolysis step, the yield is 89–91%.

8. Commercial benzene may be used.

9. The rearrangement of the azide is complete when nitrogen evolution ceases. This is usually concluded in the time indicated, but occasionally takes longer.

10. Carbon dioxide is evolved copiously at this point and may cause the solution to foam over if the acid is not added cautiously.

11. Alternatively, the solution may be poured into a 1-l. flask for this operation.

12. Solid putrescine dihydrochloride should not be heated unduly long at 100°, as it may turn pink.

3. Discussion

Putrescine dihydrochloride has been prepared by the Hofmann degradation of adipamide;[3,4,5] by the Curtius degradation of adipyl hydrazide through the urethane;[6] by the Curtius degradation of adipyl azide obtained from adipyl chloride and sodium azide;[7] by the Schmidt degradation of adipic acid with hydrogen azide;[8] by the reduction of succinonitrile,[9] succinaldoxime,[10,11] or γ-phthalimidobutyronitrile[12,13] with sodium; from N-benzoyl-γ-iodobutylamine;[14] and by the hydrolysis of 1,4-di-(N-phthalimido)butane.[15]

References and Notes

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

ethanol (64-17-5)

calcium chloride (10043-52-4)

sulfuric acid (7664-93-9)

hydrochloric acid (7647-01-0)

Benzene (71-43-2)

ether (60-29-7)

Adipic acid (124-04-9)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

carbon dioxide (124-38-9)

chlorine (7782-50-5)

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

hydrazine (302-01-2)

sodium azide (26628-22-8)

γ-phthalimidobutyronitrile

adipyl chloride (111-50-2)

diethyl adipate (141-28-6)

Putrescine dihydrochloride,
1,4-Butanediamine dihydrochloride (333-93-7)

adipyl hydrazide (1071-93-8)

adipyl azide

adipamide (628-94-4)

hydrogen azide

succinonitrile (110-61-2)

succinaldoxime

N-benzoyl-γ-iodobutylamine

1,4-di-(N-phthalimido)butane

N,N'-dicarbethoxyputrescine