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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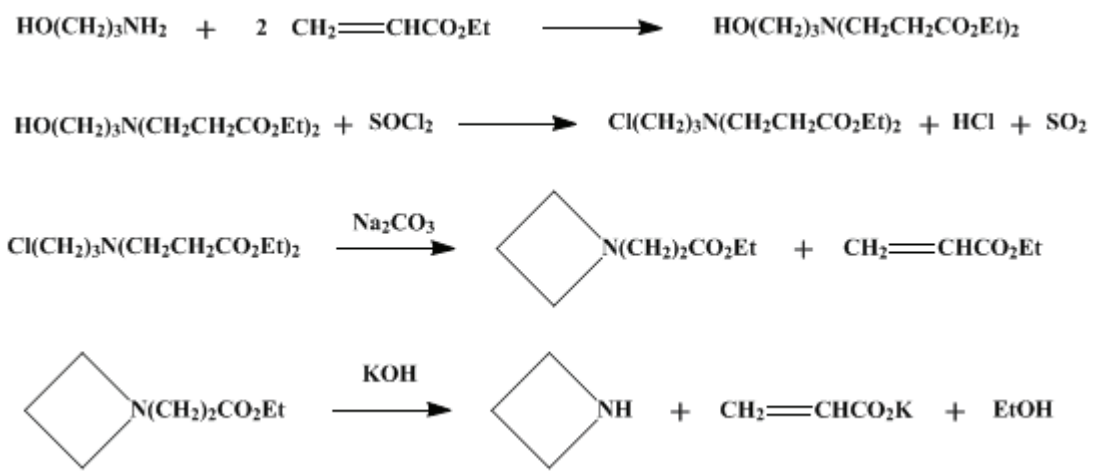
AZETIDINE



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1. Procedure

A. *Ethyl* 3-(1-*azetidinyl)propionate*. A solution of 150 g. (2.00 moles) of 3-amino-1-propanol in 500 g. (5.00 moles) of ethyl acrylate (Note 1) is refluxed for 2 hours in a 1-l., round-bottomed flask. Subsequent vacuum removal of the excess ethyl acrylate at steam temperature yields 548 g.. (99%) of crude diethyl 3-*N*-(3-hydroxypropyl)iminodipropionate. A stirred, cooled solution of this material (548 g.) in 1 l. of chloroform and 10 ml. of *N,N*-dimethylformamide is treated dropwise with 262 g. 2.20 moles) of thionyl chloride. By cooling with an ice bath and controlling the addition rate, the reaction temperature is maintained below 40° (Note 2). After the addition is complete, the reaction mixture is stirred for 30 minutes at room temperature and poured slowly into a slurry of 340 g. of sodium hydrogen carbonate in 1 l. of water (Note 3). The organic layer is separated (Note 4) and dried over sodium sulfate, and the solvent is removed under reduced pressure, below 50°, yielding 570 g. (97%) of crude diethyl 3-*N*-(3-chloropropyl)iminodipropionate. A mixture of 100 g. of this crude material, 200 g. of anhydrous, powdered sodium carbonate (Note 5), and 10.0 g. of pentaerythritol (Note 6) in 200 ml. of diethyl phthalate is placed in a 500-ml., round-bottomed flask fitted with a vacuum-distillation head and an effective stirrer. The system is evacuated through a trap of sufficient capacity to contain 50 ml. of liquid, and the product is distilled by heating the stirred suspension with a heating mantle at 10–15 mm. By proper adjustment of the heat source, the distillation temperature is maintained below 150°, minimizing codistillation of diethyl phthalate. The distillate is collected until the head temperature cannot be kept below 150°. Redistillation of the resulting crude product through a 4-in. Vigreux column yields 34.0 g. (57–68%) of ethyl 3-(1-azetidinyl)propionate, b.p. 86–87° (12 mm.), 99% pure by GC (Note 7).

B. *Azetidine*. A stirred mixture of 38 g. (0.68 mole) of potassium hydroxide pellets in 100 ml. of white mineral oil (Note 8) is heated to 140–150° in a four-necked, 500-ml., round-bottomed flask, fitted with an air-driven Hershberg stirrer, a thermometer, a dropping funnel, and a 6-in. Vigreux column fitted with a vacuum-distillation head. The flask is removed from the heat source, and 50 g. (0.32 mole) of purified ethyl 3-(1-azetidinyl)propionate is added dropwise at a rate sufficient to maintain the reaction temperature at 150° (Note 9). After addition is complete, the reaction mixture is heated to 200° at 50 mm. to remove all traces of ethanol (Note 10). The flask is fitted with a distillation head and a nitrogen bubbler, and the distillation is resumed at atmospheric pressure until azetidine distills (210° maximum pot temperature, (Note 11)). The resulting product (19.6 g., 85% purity) is dried over potassium hydroxide and redistilled through a short Vigreux column yielding 14.5–15.8 g. (80–87%) of purified azetidine, b.p. 62–63° (Note 12).

2. Notes

1. Eastman Organic Chemicals, practical grade, 3-amino-1-propanol, and ethyl acrylate were used. The checkers used 3-amino-1-propanol, Fluka purum.
2. If the reaction temperature is not controlled, a tarry by-product is formed. By dissolving the crude aminochloride in petroleum ether, the impurity is separated as an insoluble tar.
3. Considerable foaming occurs during neutralization, which is best accomplished in a 4-l. beaker with rapid stirring.
4. Any excess of insoluble salt should be filtered from the reaction mixture before the chloroform layer is separated. The checkers observed no insoluble salt at this point.
5. Baker and Adamson reagent grade sodium carbonate powder was used. The checkers found that the use of crystalline anhydrous sodium carbonate lowered the yield.
6. The presence of some hydroxylic material appears to be necessary to ensure reproducibility of this step, and the submitters have found empirically that pentaerythritol is very effective for this purpose.
7. The crude distillate can be used directly without intermediate isolation of ethyl 3-(1-azetidinyl) propionate to give a 50% yield of azetidine, assuming that all of the crude material was ethyl 3-(1-azetidinyl)propionate and running the reaction as described for the pure material.
8. Fisher Scientific Company Paraffin Oil, N.F., Saybolt Viscosity 125/135 and Mobil Oil Corp. S/V Industrial White Oil Number 320, Saybolt Viscosity 200/210 gave comparable results.
9. If the reaction does not start immediately, 5 ml. of ethanol may be added as an initiator.
10. Any ethanol that is not removed will contaminate the product. Although careful distillation will separate azetidine and ethanol, a considerable yield loss is encountered.
11. The submitters used a higher pot temperature (230–275°). The checkers, however, recommend the lower temperature to minimize losses of azetidine.
12. ^{1}H NMR ($CDCl_3$), δ 1.85 (s, 1H, N*H*), 2.0–2.6 (m, 2H, CH_2), 3.68 (t, J = 8 Hz., 2CH_2).

3. Discussion

Azetidine has been prepared by the following procedures: cyclization of 3-bromopropylamine with potassium hydroxide (low yield);[2] cleavage of 1-*p*-toluenesulfonylazetidine with sodium and refluxing 1-pentanol (85–100% yield)[3,4] or sodium and liquid ammonia (30% yield);[5] hydrogenolysis of 1-benzylazetidine (50%);[6] cyclization of diethyl 3-*N*-(3-chloropropyl)iminodipropenoate with sodium carbonate without solvent (60–70% yield).[7] A review of methods for preparing azetidine has been published.[8]

All other preparations of azetidine suffer either from low yields, arduous preparative procedures, or cumbersome purification operations. In this procedure, cyclization is accomplished in relatively concentrated solutions, and azetidine is obtained directly from the cleavage reaction in a state sufficiently pure for most applications. In addition, stable ethyl 3-(1-azetidinyl)propionate can be prepared in advance, and the air-sensitive azetidine can be formed readily as needed with a one-step procedure.

References and Notes

1. Eastman Kodak Company, Rochester, New York 14650.
2. S. Gabriel and J. Weiner, *Ber. Dtsch. Chem. Ges.*, **21**, 2669 (1888).
3. C. C. Howard and W. Markwald, *Ber. Dtsch. Chem. Ges.*, **32**, 2031 (1899).
4. W. F. Vaughn, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961). Many investigators have had difficulty in repeating this procedure. Apparently the azetidine tends to be swept out of the reaction mixture with the hydrogen.
5. A. B. Burg and C. D. Good, *J. Inorg. Nucl. Chem.*, **2**, 237 (1956).
6. R. S. Klonowski, Ph.D. Dissertation, University of Michigan, 1959.
7. D. H. Wadsworth, *J. Org. Chem.*, **32**, 1184 (1967). Although this procedure will furnish good yields on a small scale, scale-up causes mechanical difficulties and lower yields.
8. James A. Moore, in "The Chemistry of Heterocyclic Compounds," Vol. 19, Part II, A.

Weissberger, Ed., Interscience, New York, 1964, Chap. VII.

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

petroleum ether

diethyl 3-N-(3-hydroxypropyl)iminodipropionate

diethyl 3-N-(3-chloropropyl)iminodipropionate

diethyl 3-N-(3-chloropropyl)iminodipropenoate

ethanol (64-17-5)

ammonia (7664-41-7)

hydrogen (1333-74-0)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

sodium hydrogen carbonate (144-55-8)

sodium carbonate (497-19-8)

sodium sulfate (7757-82-6)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

ethyl acrylate (140-88-5)

Pentaerythritol (115-77-5)

1-pentanol (71-41-0)

N,N-dimethylformamide (68-12-2)

diethyl phthalate (84-66-2)

Azetidine (503-29-7)

3-amino-1-propanol (156-87-6)

ethyl 3-(1-azetidinyl)propionate (7730-42-9)

3-bromopropylamine (5003-71-4)

1-benzylazetidine

1-p-toluenesulfonylazetidine (7730-45-2)