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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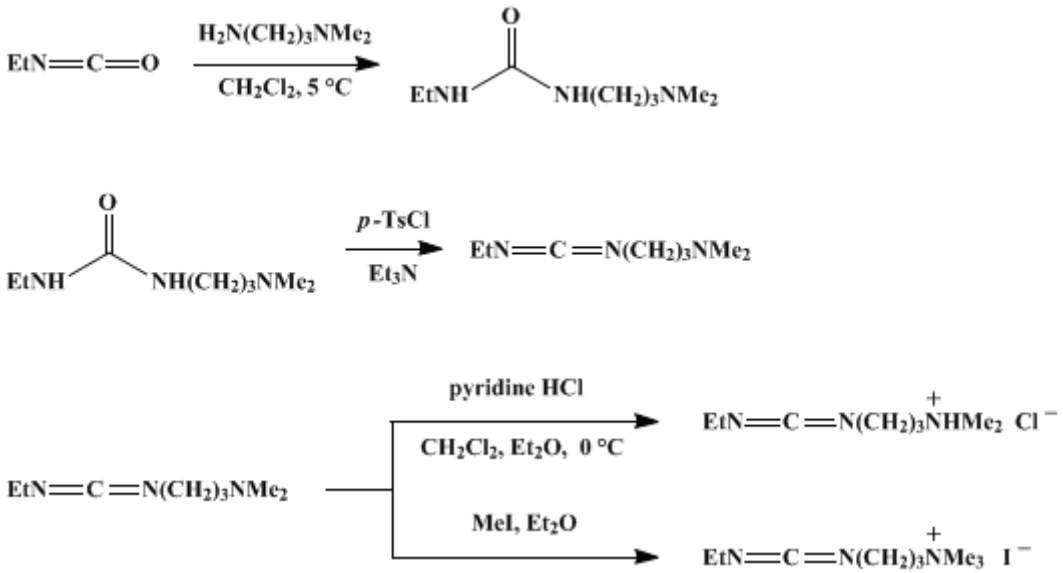
1-ETHYL-3-(3-DIMETHYLAMINO)PROPYLCARBODIIMIDE HYDROCHLORIDE AND METHIODIDE

[Carbodiimide, [3-(dimethylamino)propyl]ethyl-, hydrochloride and Ammonium iodide, [3-[[(ethylimino)methylene]amino]propyl]trimethyl-]



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1. Procedure

A. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide*. A solution of 100 g. (1.41 moles) of ethyl isocyanate (Note 1) in 750 ml. of methylene chloride is prepared in a 5-l. three-necked flask equipped with a mechanical stirrer, an immersion thermometer, and a 500-ml., pressure-equalizing, addition funnel (Note 2). The flask and its contents are cooled to 5° in an ice bath, and a solution of 144 g. (1.41 moles) of N,N-dimethyl-1,3-propanediamine in 250 ml. of methylene chloride is added through the addition funnel at a rate such that the reaction temperature does not exceed 10° (Note 3). On completion of this addition 500 ml. of triethylamine is added to the flask, and a solution of 300 g. (1.6 moles) of *p*-toluenesulfonyl chloride in 300 ml. of methylene chloride is placed in the addition funnel and added to the reaction mixture, again at a rate such that the temperature does not exceed 10° (Note 4). After completion of the second addition, the ice bath is replaced with a heating mantle and the addition funnel with a reflux condenser; the reaction mixture is then heated under gentle reflux for 3 hours. Anhydrous sodium carbonate (400 g.) is added to the cooled reaction mixture, followed by 3.5 l. of ice water. The mixture is stirred vigorously for 30 minutes, after which the phases are allowed to separate, and the lower, organic phase is drawn off through a tube into a 2-l. suction flask. The aqueous phase is then extracted with three 500-ml. portions of methylene chloride (Note 5). The original methylene chloride phase and the extracts are combined and dried over anhydrous magnesium sulfate. The solvents are removed under reduced pressure, and the dark brown residue is distilled under reduced pressure through a 15-cm. Vigreux column to give 1-ethyl-3-(3-dimethylamino)propylcarbodiimide, b.p. 52–55° (0.3–0.4 mm.), n^{25}D 1.4591. The yield is 110–118 g. (50–54%) (Note 6).

B. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride*. A suspension of 34.6 g. (0.300 mole) of pyridine hydrochloride (Note 7) in 280 ml. of methylene chloride is prepared in a 1-l. Erlenmeyer flask. To this is slowly added 46.5 g. (0.300 mole) of 1-ethyl-3-(3-dimethylamino) propylcarbodiimide. The resulting solution is diluted with anhydrous ether (Note 8) and stored at 0–5°

for 16–20 hours. The crystalline product is collected by filtration in a *dry* atmosphere (Note 9), washed with a little anhydrous ether, and dried under reduced pressure over phosphorus pentoxide. The yield is 50.5–55.5 g. (88–96.5%), m.p. 104–109° (Note 10) and (Note 11). This material is sufficiently pure for most purposes.

C. *1-Ethyl-3-(3-dimethylamino)propylcarbodiimide methiodide*. A solution of 30.0 g. (0.193 mole) of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide in 750 ml. of anhydrous ether is prepared in a 2-l. Erlenmeyer flask. To this is slowly added from an addition funnel a solution of 30.0 g. (0.21 mole) of methyl iodide in 100 ml. of ether. The mixture is stored in the dark for 48 hours, after which the crystalline product is collected by filtration, washed with ether, and dried. The product, m.p. 94–95°, weighs 50.5–52.5 g. (88–91.5%) (Note 12).

2. Notes

1. Available from Eastman Organic Chemicals.
2. The assembled apparatus was dried at 120° for 18 hours.
3. The addition time was *ca.* 2 hours.
4. The addition time was *ca.* 3 hours.
5. Extractions were carried out in the reaction flask; after separation, the lower, methylene chloride phase was drawn off by suction.
6. The submitters, working on a twofold scale, obtained a yield of 60–65%.
7. Pyridine hydrochloride is extremely hygroscopic; the material used must be the anhydrous crystalline form.
8. Vigorous boiling of solvent occurs during addition of the carbodiimide and during spontaneous crystallization of the product. Approximately 250 ml. of ether was used.
9. The product is hygroscopic and care must be taken to protect it from atmospheric moisture at all times.
10. A sample of analytical purity had m.p. 113.5–114.5°.
11. The submitters, working on a 4.5-fold scale, obtained 92% of product, m.p. 108–112°.
12. The submitters, working on a twofold scale, obtained 95.5% of product, m.p. 93–95°, after one recrystallization from chloroform-ether.

3. Discussion

This procedure for the preparation of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide and its salts is a modification of one that has been published.[2] Unsymmetrical carbodiimides have also been prepared by desulfurization of the corresponding thioureas with mercuric oxide[3] or by dehydration of the corresponding ureas with *p*-toluenesulfonyl chloride in pyridine.[4] Unsymmetrical 1,3-disubstituted ureas are best prepared by the reaction of isocyanates with primary or secondary amines[5] or by the action of carbamoyl chlorides on primary or secondary amines.[6]

4. Merits of the Preparation

Carbodiimides are, in general, useful compounds for effecting certain dehydrative condensations, *e.g.*, in the formation of amides, esters, and anhydrides. These two crystalline water-soluble carbodiimides are especially useful in the synthesis of peptides and in the modification of proteins. The excess of reagent and the co-product (the corresponding urea) are easily separated from products with limited solubility in water. The hydrochloride is best employed in nonaqueous solvents (methylene chloride, acetonitrile, dimethylformamide). The methiodide is relatively stable in neutral aqueous systems, and thus is recommended for those media.

Preparation of carbodiimides by dehydration of the corresponding ureas is of general applicability and is well adapted to the laboratory preparation of substantial quantities. The intermediates for this particular preparation are commercially available at moderate cost.

References and Notes

1. Research Institute for Medicine and Chemistry, Cambridge, Massachusetts 02142.
2. J. C. Sheehan, P. A. Cruickshank, and G. L. Boshart, *J. Org. Chem.*, **26**, 2525 (1961).
3. H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).
4. G. Amiard and R. Heymès, *Bull. Soc. Chim. France*, 1360 (1956).
5. V. Papesch and E. F. Schroeder, *J. Org. Chem.*, **16**, 1879 (1951).
6. E. N. Abrahart, *J. Chem. Soc.*, 1273 (1936).

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

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride and methiodide

ether (60-29-7)

acetonitrile (75-05-8)

chloroform (67-66-3)

sodium carbonate (497-19-8)

mercuric oxide (21908-53-2)

pyridine (110-86-1)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

pyridine hydrochloride (628-13-7)

dimethylformamide (68-12-2)

triethylamine (121-44-8)

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide (1892-57-5)

Carbodiimide, [3-(dimethylamino)propyl]ethyl-, hydrochloride,
1-Ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride (25952-53-8)

Ammonium iodide, [3-[[(ethylimino)methylene]amino]propyl]trimethyl-

ethyl isocyanate (109-90-0)

N,N-dimethyl-1,3-propanediamine (109-55-7)

p-Toluenesulfonyl chloride (98-59-9)

phosphorus pentoxide (1314-56-3)

1-Ethyl-3-(3-dimethylamino)propylcarbodiimide methiodide (22572-40-3)