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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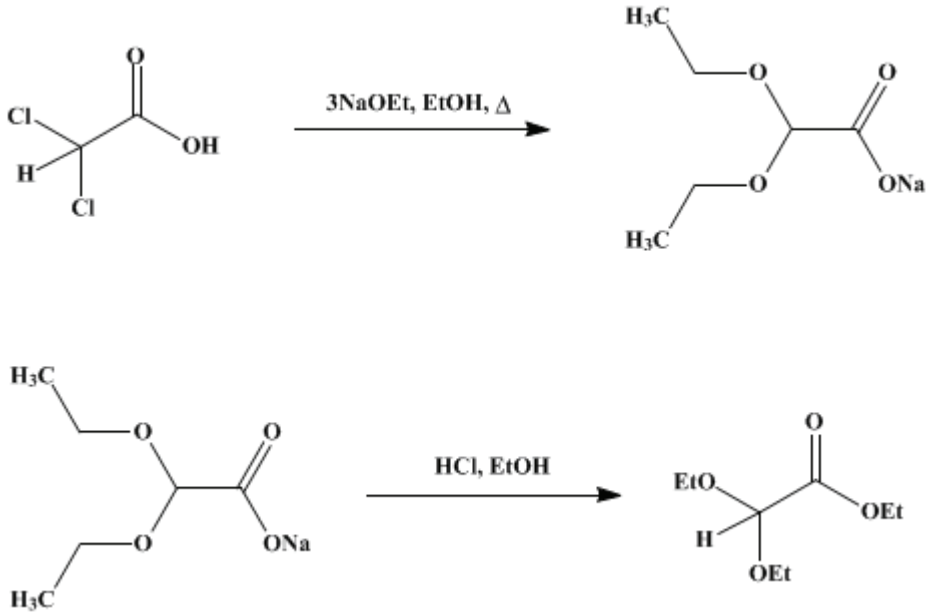
ETHYL DIETHOXYACETATE

[Glyoxylic acid, ethyl ester, diethyl acetal]



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1. Procedure

A 2-l. three-necked flask (Note 1), fitted with a sealed stirrer (Note 2) and an efficient reflux condenser (protected by a calcium chloride tube), is surrounded by a water bath. Sodium ethoxide is prepared in this flask by adding 31 g. (1.35 g. atoms) of sodium in portions to 450 ml. of absolute ethanol (Note 3). When practically all the sodium has dissolved, 50 g. (0.39 mole) of dichloroacetic acid is added with stirring at such a rate that the solvent refluxes smoothly. About 20 minutes is required. Sodium chloride soon begins to separate, and the solution becomes a yellow-orange color. After the initial reaction subsides, the mixture is heated under reflux with stirring for 3.5 hours.

The water is removed from the water bath and replaced by an ice-salt mixture. A thermometer is placed in the flask with the bulb below the surface of the liquid, and the mixture is cooled below 0°. Then a solution of about 27 g. (0.75 mole) of hydrogen chloride in 200 ml. of absolute ethanol (Note 4) is slowly added (Note 5) during about 40 minutes with stirring and cooling at such a rate that the temperature does not rise above 10°. The mixture is allowed to come to room temperature, and the stirring is continued for 3 hours. It is then allowed to stand overnight. The reaction mixture is again cooled to 0°, and the excess acid is neutralized to approximately pH 7 by slowly adding sodium ethoxide solution (Note 6). The mixture is tested from time to time during the addition of the alkali by placing a drop on moistened pH test paper. About 75 ml. of sodium ethoxide solution is required. The mixture is then filtered through a large Büchner funnel (Note 7), and the precipitate is extracted thoroughly with ether which is added to the alcoholic filtrate. The solid is discarded.

Most of the solvent is removed by distillation through a Vigreux column under reduced pressure (about 40 mm.) and a pot temperature less than 40°. The product is then transferred to a smaller flask (Note 8). The remainder of the solvent is removed through the Vigreux column at a pressure of about 15 mm. and a boiling point up to about 40°. A Dry Ice-cooled receiver (Note 9) is then attached, and the pressure is lowered by means of a high-vacuum pump. The crude product is distilled until no more material comes over while the flask is heated on a steam bath. This crude product, b.p. 87–88°/17 mm.,

69–70°/10 mm., n_D 1.4073–1.4076, may be redistilled, a pinch of calcium carbonate being added, through an efficient column (Note 10) at a pressure of about 12 mm. The fore-run (boiling point up to about 60°/12 mm.) is discarded. The fraction, b.p. 60–81°/12 mm., is saved for redistillation with a subsequent run. The main fraction is obtained at a boiling range of 81–83°/12 mm. The yield of ethyl diethoxyacetate is 31–34 g. (45–50%) of colorless liquid, n_D^{25} 1.4075.

2. Notes

1. The submitter reports equally satisfactory results when the reaction is carried out in a 12-l. flask on ten times the scale described here.
2. A Hershberg stirrer is excellent for the purpose and may be connected by a mercury seal or a rubber seal[2] lubricated with glycerol (p. 546).
3. The absolute ethanol is dried with sodium and diethyl phthalate.[3]
4. The alcoholic hydrogen chloride can be prepared by passing hydrogen chloride from a cylinder (use safety trap) into 200 ml. of absolute ethanol cooled by an ice bath. From time to time a sample may be withdrawn and titrated with standard alkali to determine the concentration. The exact amount is not critical, but a considerable excess of hydrogen chloride must be used. If several runs are to be made it is convenient to prepare a large quantity of alcoholic hydrogen chloride at one time.
5. Precautions should be taken to prevent absorption of atmospheric moisture by the hydrogen chloride solution. The dropping funnel should be closed or protected by a calcium chloride tube.
6. Enough sodium ethoxide solution for four runs can be made in a 500-ml. flask by adding 18.4 g. of sodium portionwise to 300 ml. of absolute ethanol.
7. If difficulty in the filtration is encountered a filter aid may be used.
8. At this point it is convenient to combine several runs for distillation.
9. The Dry Ice-cooled receiver is conveniently constructed from a two-necked round-bottomed flask immersed up to the necks in a Dry Ice-ethanol mixture.
10. The submitter used a column packed with 12 in. of 1/8-in. glass helices and fitted with a variable reflux head. The checkers used a 12-in. Vigreux column.

3. Discussion

Ethyl diethoxyacetate has been prepared from dichloroacetic acid by the action of sodium ethoxide followed by esterification of the intermediate diethoxyacetic acid. This esterification has been carried out with ethyl iodide on the sodium salt or on the silver salt.[4,5,6] It has been more conveniently done with ethanol and acid.[7,8,9] Poorer yields are reported when the dichloroacetic acid is first esterified and then treated with sodium ethoxide.[10] Ethyl diethoxyacetate also has been prepared by the reaction of ethanol with the hemiacetal of ethyl glyoxylate in the presence of hydrogen chloride,[11] and by the treatment of 1,2-diethoxy-1,1,2-trichloroethane or 1,2-diethoxy-1-chloroethane with ethanol in the presence of pyridine.[12]

References and Notes

1. The Upjohn Company, Kalamazoo, Michigan.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Glyoxylic acid, ethyl ester, diethyl acetal

hemiacetal of ethyl glyoxylate

ethanol (64-17-5)

hydrogen chloride (7647-01-0)

ether (60-29-7)

glycerol (56-81-5)

sodium chloride (7647-14-5)

calcium carbonate (471-34-1)

pyridine (110-86-1)

sodium (13966-32-0)

sodium ethoxide (141-52-6)

dichloroacetic acid (79-43-6)

Ethyl iodide (75-03-6)

diethyl phthalate (84-66-2)

Ethyl diethoxyacetate (6065-82-3)

diethoxyacetic acid

1,2-diethoxy-1,1,2-trichloroethane

1,2-diethoxy-1-chloroethane