



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.

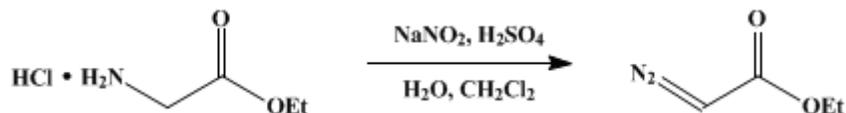
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 4, p.424 (1963); Vol. 36, p.25 (1956).

ETHYL DIAZOACETATE

[Acetic acid, diazo-, ethyl ester]



Submitted by N. E. Searle¹

Checked by Melvin S. Newman, G. F. Ottmann, and C. F. Grundmann.

1. Procedure

Diazoacetic esters are potentially explosive and therefore must be handled with caution. They are also toxic and prone to cause development of specific sensitivity. A well-ventilated hood should be used for the entire procedure.

A solution of 140 g. (1 mole) of ethyl glycinate hydrochloride² in 250 ml. of water is mixed with 600 ml. of methylene chloride in a 2-l. four-necked round-bottomed flask fitted with a stirrer, dropping funnel, thermometer, and nitrogen inlet tube, and cooled to -5° (Note 1). The flask is flushed with nitrogen and an ice-cold solution of 83 g. (1.2 moles) of sodium nitrite in 250 ml. of water is added with stirring. The temperature is lowered to -9° (Note 1), and 95 g. of 5% (by weight) sulfuric acid is added from the dropping funnel during a period of about 3 minutes (Note 2). The temperature may rise to a maximum of $+1^\circ$ with the cooling bath at -23° (Note 3). The reaction terminates within 10 minutes, when heat is no longer evolved.

The reaction mixture is transferred to an ice-cold 2-l. separatory funnel, and the yellow-green methylene chloride layer is run into 1 l. of cold 5% sodium bicarbonate solution. The aqueous layer is extracted once with 75 ml. of methylene chloride. The methylene chloride and sodium bicarbonate solutions are returned to the separatory funnel and shaken until no trace of acid remains, as shown by indicator paper (Note 4). The golden yellow organic layer is separated, transferred to a dry separatory funnel, and shaken for 5 minutes with 15 g. of granular anhydrous sodium sulfate. The dried ethyl diazoacetate solution is filtered through a cotton plug inserted in the separatory funnel stem, and the bulk of the solvent is distilled through an efficient column at a pressure of about 350 mm. (Note 5). The last traces of solvent are removed at a pressure of 20 mm. and a maximum pot temperature of 35° (Note 6). The yield is 90–100 g. (79–88%) of yellow oil, n_D^{25} 1.462. This product is pure enough for most synthetic work (Note 7) and (Note 8).

2. Notes

1. Lower temperatures may induce the solid methylene chloride dihydrate to separate and interfere with stirring. An acetone bath into which lumps of Dry Ice are introduced as required affords easily controlled cooling.
2. The stated amount of acid has been found sufficient to provide the strongly acidic medium which the reaction requires.
3. Higher reaction temperatures may result in reduced yields.
4. Traces of acid must be eliminated before the diazoacetate solution is concentrated.
5. Efficient solvent separation is indicated by absence of yellow color in the distillate. An 18-in. column packed with Berl saddles is satisfactory.
6. Higher temperatures should be avoided because of the explosive character of ethyl diazoacetate. The product should be placed in dark brown bottles and kept in a cool place. It should be used as soon as possible.
7. Distillation through a 7-in. column packed with glass helices gives a 65% over-all yield, b.p. $29-31^\circ/5$ mm. *Anal.* Calcd. for $\text{C}_4\text{H}_6\text{N}_2\text{O}_2$: N, 24.55. Found: N, 24.76. Heart-cut material has a refractive index of n_D^{25} 1.4616.³ Principal loss is due to elimination of nitrogen with formation of high-boiling

esters. Both the crude and the distilled products appear to function equally well as synthetic intermediates. *Distillation, even under reduced pressure, is dangerous, for the substance is explosive.* 8. The procedure has proved satisfactory for the preparation of the methyl, butyl, *n*-hexyl, 2-ethylhexyl, and decyl esters of diazoacetic acid.⁴ *The methyl ester should be handled with particular caution since heat causes it to detonate with extreme violence.*

3. Discussion

Ethyl diazoacetate has been prepared from sodium nitrite and ethyl glycinate hydrochloride in the presence of diethyl ether.⁵ The present procedure utilizes the unique ability of methylene chloride solvent to protect the diazoacetic ester from decomposition by aqueous mineral acid.⁴ Hammond claims that the use of halogenated hydrocarbons, such as carbon tetrachloride, leads to a 95% yield of ethyl diazoacetate.⁶

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 258
- Org. Syn. Coll. Vol. 6, 913
- Org. Syn. Coll. Vol. 7, 438

References and Notes

1. Contribution No. 360 from the Chemical Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware.
2. *Org. Syntheses Coll. Vol. 2*, 310 (1943).
3. Data obtained by V. A. Engelhardt and H. E. Cupery.¹
4. Searle (to E. I. du Pont de Nemours and Company), U. S. pat. 2,490,714 [*C. A.*, **44**, 3519 (1950)].
5. *Org. Syntheses Coll. Vol. 3*, 392 (1955).
6. Hammond (to National Distillers Products Corp.), U. S. pats. 2,691,649 and 2,691,650 [*C. A.*, **49**, 11690 (1955)].

Appendix

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

methyl, butyl, *n*-hexyl, 2-ethylhexyl, and decyl esters

sulfuric acid (7664-93-9)

diethyl ether (60-29-7)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

sodium nitrite (7632-00-0)

methylene chloride (75-09-2)

ethyl diazoacetate,
Acetic acid, diazo-, ethyl ester (623-73-4)

ethyl glycinate hydrochloride (623-33-6)

methylene chloride dihydrate

diazoacetate,
diazoacetic acid