



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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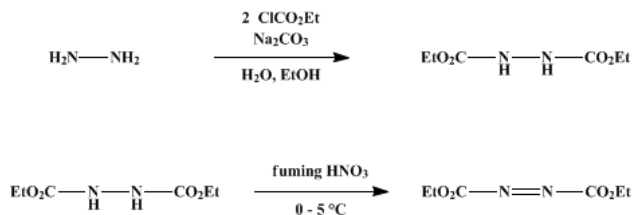
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

ETHYL AZODICARBOXYLATE

[Formic acid, azodi-, diethyl ester]



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Checked by William G. Dauben and Robert L. Cargill.

1. Procedure

A. *Ethyl hydrazodicarboxylate*. In a 3-l., three-necked flask equipped with a mechanical stirrer, two 500-ml. dropping funnels, and a thermometer (Note 1), is placed a solution of 75 g. (1.5 moles) of 100% hydrazine hydrate (or 88.5 g. of 85% hydrazine hydrate) in 750 ml. of 95% ethanol. The reaction flask is cooled in an ice bath. When the solution temperature drops to 10°, 326 g. (3 moles) of ethyl chloroformate is added dropwise with stirring at a rate sufficient to maintain the temperature between 15° and 20°. After exactly one-half of the ethyl chloroformate has been introduced, a solution of 159 g. (1.5 moles) of sodium carbonate in 750 ml. of water is added dropwise simultaneously with the remaining ethyl chloroformate. The addition of these two reactants is regulated so that the temperature does not rise above 20°. The addition of the chloroformate should be completed slightly in advance of the sodium carbonate, thus maintaining an excess of the chloroformate in the solution at all times. During the course of the addition of the reagents, a precipitate is formed.

After addition of the reactants is complete, the walls of the flask are washed down with 200 ml. of cold water, and the reaction mixture is allowed to stir for 30 minutes. The precipitate is then collected on a Büchner funnel, washed well with a total of 1 l. of cold water, and dried in a vacuum oven at 80°. There is obtained 215–225 g. (81–85%) of ethyl hydrazodicarboxylate which melts at 131–133°. It is sufficiently pure for the preparation of ethyl azodicarboxylate (Note 2) and (Note 3).

B. *Ethyl azodicarboxylate*. **Caution! Both ethyl and methyl azodicarboxylate are sensitive to heat. Thus, in a sealed capillary they explode violently when heated by a flame. Overheating is to be avoided, and distillations should be from a bath, not an electrically heated mantle. Distillations should be well shielded. Since copious fumes of nitrogen oxides are evolved during the oxidation by nitric acid, this operation and the subsequent work-up should be carried out in an efficient hood.**

A mixture of 200 g. of ethyl hydrazodicarboxylate in 125 ml. of 70% nitric acid is placed in a 1-l., three-necked flask equipped with a mechanical stirrer, gas-outlet tube, and thermometer. The flask is cooled in an ice bath, and when the temperature of the solution reaches 5°, 220 ml. of ice-cold yellow fuming nitric acid (90–95% HNO₃, *d*₁₅ = 1.49–1.50) is added. The reaction mixture is maintained at 0–5° for 2 hours with stirring and is then carefully poured on a stirred mixture of 500 g. of ice, 500 ml. of ice water, and 100 ml. of methylene chloride in a 2-l. beaker placed in a metal pan (Note 4). After the ice melts, the solution is transferred carefully to a 2-l. separatory funnel. The organic (lower) layer is removed, and the acid layer is extracted (Note 5) with three 100-ml. portions of methylene chloride. The combined organic layers are washed twice with 100-ml. portions of ice water and are then stirred mechanically for 10 minutes with 500 ml. of ice-cold 10% potassium bicarbonate solution. The layers are separated in a separatory funnel, and the organic layer is finally washed with 100 ml. of ice water and dried quickly with a small portion of anhydrous magnesium sulfate that is removed by filtration. The solution is dried overnight with a fresh portion of anhydrous magnesium sulfate. **Caution! The following distillations should be well shielded.** The methylene chloride is removed on a steam bath under reduced pressure, and the residue is rapidly distilled without fractionation under vacuum (1–5 mm.) from a flask immersed in an oil bath whose temperature is raised gradually from 75° to 130°. The crude distillate is then fractionally distilled under vacuum through a short column packed with glass helices, using an oil bath to heat the distillation flask. After a short fore-run, the main fraction is collected at 93–95°/5 mm. There is obtained 138–158 g. (70–80%) of ethyl azodicarboxylate which freezes at 6° (Note 6), (Note 7), and (Note 8).

2. Notes

1. The thermometer and one of the funnels are fitted to a two-necked adapter so that, when the thermometer bulb is immersed in the solution, the range between 10° and 20° is easily visible.

2. Ethyl hydrazodicarboxylate may be purified by crystallization from dilute ethanol; m.p. 134–135°.

3. Methyl hydrazodicarboxylate, which is much more soluble in water than the ethyl ester, may be prepared by the following modification of the above procedure.

A solution of 100 g. (2 moles) of hydrazine hydrate in 500 ml. of 95% alcohol is treated as described above with a total of 378 g. (4 moles) of methyl chloroformate while maintaining the temperature below 20°. During the addition of the last half of the chloroformate, a warm (30–35°) solution of 212 g. (2 moles) of sodium carbonate in 800 ml. of water is added. The resulting slurry is stirred for 30 minutes, and the precipitate is filtered on a Büchner funnel, washed with 100 ml. of ice water, and air-dried. The filtrate is concentrated at reduced pressure (12–25 mm.) on a water bath to 700 ml. and is cooled in ice. The precipitate is filtered, washed with 100 ml. of ice water, and air-dried. The combined crops of crude methyl hydrazodicarboxylate are dried at 60° in a vacuum oven and are then stirred successively with two 800-ml. portions of warm acetone to separate inorganic impurities. The acetone solution is filtered, and evaporated at reduced pressure to yield 260 g. (88%) of methyl hydrazodicarboxylate (m.p. 127–131°) of sufficient purity for preparation of methyl azodicarboxylate.

A purer product (m.p. 131–132°) may be obtained by warming the acetone solution to 50° and adding to it 1.8 l. of hexane or heptane also warmed to 50°. The solution is seeded and allowed to cool slowly.

4. As a safety precaution, in case the beaker should break, it is placed in a metal pan.

5. The separatory funnel should be carefully vented at frequent intervals since large quantities of nitrogen oxides are liberated.

6. The submitter found that methyl azodicarboxylate can be prepared by a modification of this procedure. It is somewhat more water-soluble and much more susceptible to hydrolysis than the ethyl ester.

A mixture of 200 g. (1.35 moles) of methyl hydrazodicarboxylate, 400 ml. of chloroform (washed with water and dried over calcium chloride), and 250 ml. of concentrated nitric acid is cooled to 5°, and 350 ml. of ice-cold yellow fuming (90–95%) nitric acid is added. The solution is stirred for 2 hours at 0–5° and is poured onto 1 kg. of crushed ice. After most of the ice has melted, the organic layer is separated (Note 5) and is washed quickly with two 500-ml. portions of ice water containing some ice. It is then stirred for 2 minutes with a mixture of 300 ml. of ice-cold 10% potassium bicarbonate solution and 200 g. of crushed ice. The organic layer is separated, washed quickly with ice water, and dried and distilled as described for the ethyl ester. There is obtained 148 g. (75%) of methyl azodicarboxylate which boils at 90–91°/15 mm. and freezes at 10° (Note 7).

7. The submitter has found that methyl azodicarboxylate is often more reactive than the ethyl ester. Moreover, adducts prepared from the methyl ester are generally higher melting and lower boiling than those from the ethyl ester, and thus more easily purified.

8. A frequent annoying by-product of the reactions of azodicarboxylic esters is the corresponding hydrazodicarboxylate. In the case of the methyl ester this impurity is easily removed because of its moderate solubility in water and low solubility in such solvents as carbon tetrachloride.

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3. Discussion

Ethyl hydrazodicarboxylate has been prepared by the reaction of ethyl chloroformate with hydrazine hydrate² or hydrazine sulfate in the presence of alkali.³

Ethyl azodicarboxylate has been prepared by oxidation of ethyl hydrazodicarboxylate with hypochlorous acid,⁴ concentrated nitric acid,³ and a mixture of concentrated and fuming nitric acid.^{5,6}

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 544

References and Notes

1. Contribution No. 633, from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Co., Wilmington, Delaware.
2. Curtius and Heidenreich, *J. prakt. Chem.*, **52**, 476 (1895); Voegelé, *Rec. trav. chim.*, **65**, 789 (1946).
3. Ingold and Weaver, *J. Chem. Soc.*, **127**, 381 (1925).
4. Rabjohn, *Org. Syntheses Coll. Vol.* **3**, 375 (1955).
5. Curtius and Heidenreich, *Ber.*, **27**, 774 (1894).
6. Diels and Fritzsche, *Ber.*, **44**, 3018 (1911).

Appendix

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

nitrogen oxides
ethyl and methyl azodicarboxylate
ethanol (64-17-5)
calcium chloride (10043-52-4)
chloroform (67-66-3)
nitric acid (7697-37-2)
sodium carbonate (497-19-8)
carbon tetrachloride (56-23-5)
acetone (67-64-1)
hypochlorous acid (7790-92-3)
hydrazine hydrate (7803-57-8)
Hydrazine sulfate (10034-93-2)
methylene chloride (75-09-2)
ethyl chloroformate (541-41-3)
magnesium sulfate (7487-88-9)
chloroformate
heptane (142-82-5)
methyl chloroformate (79-22-1)
Ethyl azodicarboxylate
Formic acid, azodi-, diethyl ester (1972-28-7)
Ethyl hydrazodicarboxylate
hexane (110-54-3)
methyl azodicarboxylate
potassium bicarbonate (298-14-6)
Methyl hydrazodicarboxylate
hydrazodicarboxylate