



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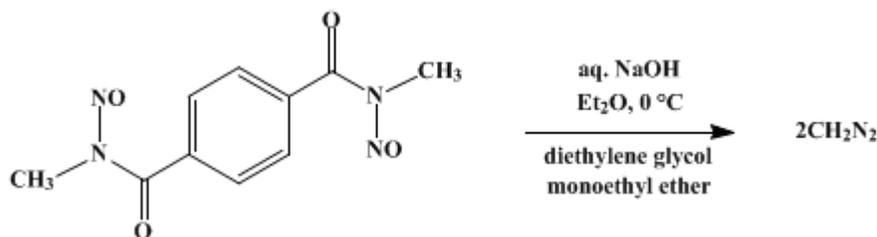
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 5, p.351 (1973); Vol. 41, p.16 (1961).

DIAZOMETHANE

[Methane, diazo-]



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Checked by D. J. Pasto and E. J. Corey.

1. Procedure

Caution! Diazomethane is toxic and explosive. The operation must be carried out in a good hood with an adequate shield (Note 1).

An efficient condenser (60 cm. or longer) is fitted with an adapter to which is sealed a length of 9-mm. tubing extending nearly to the bottom of a 5-l. round-bottomed flask, which serves as the distillation receiver (Note 2) and (Note 3). The adapter should be connected to the receiver with a two-hole stopper carrying a drying tube if anhydrous diazomethane is desired. The receiver is placed in a well-mixed ice-salt mixture, and sufficient anhydrous ether (about 200 ml.) is added to cover the tip of the adapter.

In a 5-l. round-bottomed flask are placed 3 l. of U.S.P. solvent grade ether, 450 ml. of diethylene glycol monoethyl ether (Note 4), and 0.6 l. of 30% aqueous sodium hydroxide solution (Note 5). The mixture is chilled in an ice-salt bath to 0° (Note 6), and 180 g. (0.5 mole) of N,N'-dimethyl-N,N'-dinitrosoterephthalamide (70% in mineral oil) (Note 7) is added in one portion. The flask is immediately transferred to a heating mantle and connected by a gooseneck to the condenser. The yellow color of diazomethane appears in the receiver almost immediately. About 2 l. of ether is distilled in 2–2.5 hours (Note 8); the distilling ether is practically colorless at this point. The tip of the adapter should be kept just below the surface of the distillate during the distillation. The distillate contains 0.76–0.86 mole (76–86%) (Note 9) and (Note 10) of diazomethane as determined by titration.² When the apparatus has been protected with a drying tube, the diazomethane is suitable for reaction with an acid chloride without further drying.

2. Notes

1. Diazomethane is not only toxic but also potentially explosive. Hence one should wear heavy gloves and goggles and work behind a safety screen or a hood door with safety glass, as is recommended in the preparation of diazomethane described by De Boer and Backer.³ As is also recommended there, ground joints and sharp surfaces should be avoided. Thus all glass tubes should be carefully fire-polished, connections should be made with rubber stoppers, and separatory funnels should be avoided, as should etched or scratched flasks. Furthermore, at least one explosion of diazomethane has been observed at the moment crystals (sharp edges!) suddenly separated from a supersaturated solution. Stirring by means of a Teflon-coated magnetic stirrer is greatly to be preferred to swirling the reaction mixture by hand, for there has been at least one case of a chemist whose hand was injured by an explosion during the preparation of diazomethane in a hand-swirled reaction vessel.

It is imperative that diazomethane solutions not be exposed to direct sunlight or placed near a strong artificial light because light is thought to have been responsible for some of the explosions that have

been encountered with **diazomethane**. Particular caution should be exercised when an organic solvent boiling higher than **ether** is used. Because such a solvent has a lower vapor pressure than **ether**, the concentration of **diazomethane** in the vapor above the reaction mixture is greater and an explosion is more apt to occur.

Most **diazomethane** explosions occur during its distillation. Hence **diazomethane** should not be distilled unless the need justifies it. An **ether** solution of **diazomethane** satisfactory for many uses can be prepared as described by Arndt,² where **nitrosomethylurea** is added to a mixture of **ether** and 50% aqueous **potassium hydroxide** and the **ether** solution of **diazomethane** is subsequently decanted from the aqueous layer and dried over **potassium hydroxide pellets** (not sharp-edged sticks!). When distilled **diazomethane** is required, the alternative procedure of De Boer and Backer³ is particularly good because at no time is much **diazomethane** present in the distilling flask.

Both the toxicity and explosion hazards associated with **diazomethane** are discussed by Gutsche.⁴

2. If it is desired to determine the yield of **diazomethane** by titration, the receiver should be calibrated so that the volume of the distillate can be measured without the necessity of transferring to a graduated vessel.

3. The submitters have used equipment having all connections made with ungreased 29 / 42 ground-glass joints. This is contrary to previously recommended practice (Note 1). The submitters feel that ground-glass joints do not represent an added hazard, and that their use expedites the completion of consecutive runs. In the course of many preparations, however, a film of polymethylene was found to accumulate on the joints and prevent a tight fit. This film can be removed by a brief treatment with hot concentrated alkali and vigorous rubbing.

In some forty preparations made by the submitters, one explosion occurred which was attributed to the cracking of the adapter tube during the distillation. The adapter and the drying tube were disintegrated, but the receiver and the contents of the distilling flask were not affected, indicating a local detonation that was not sustained.

The checkers did not use glassware with ground-glass joints. New unmarked flasks and condenser were used which were connected together with fire-polished glass tubing and rubber stoppers.

4. Practical grade **2-(2-ethoxyethoxy)ethanol** (Matheson, Coleman and Bell) can be used without further treatment. In a few preparations, the submitters encountered difficulty with the formation of a very stiff gel of **disodium terephthalate** in the flask during distillation. In one case, this difficulty was traced to the use of an old bottle of **2-(2-ethoxyethoxy)ethanol** from another source.

This relatively large volume of cosolvent was found to give optimum yields. The submitters have found that the evolution of **diazomethane** from a stirred suspension of the reagent in **ether** and 40% aqueous **sodium hydroxide** is extremely slow and incomplete.

5. The use of more concentrated solutions of **potassium hydroxide** gave somewhat lower yields.

6. *Caution! It is extremely important that the flask contents be cooled to at least 0°. The reaction is rapid and a considerable amount of diazomethane is generated at this temperature.*

7. This material is available from Eastman Organic Chemicals and Aldrich Chemical Company. It is also available from E. I. du Pont de Nemours and Company, who use the trade name Nitrosan for it. The 30% white mineral oil acts as a stabilizer. The material may be stored indefinitely at room temperature. It sometimes turns green on long standing, but this does not affect the yield of **diazomethane** (private communication from B. C. McKusick).

8. The yield of **diazomethane** is slightly lower if the distillation is carried out more slowly.

9. The average yield in some thirty runs was over 80%; yields as high as 95% have been obtained. It is probable that a second receiver in series would permit the recovery of a small additional amount of **diazomethane**.

10. The checkers decomposed the small amount of **diazomethane** remaining in the reaction flask by careful addition of 100 ml. of **acetic acid** before disposal.

3. Discussion

Diazomethane has been prepared by the action of base on **nitrosomethylurea**,² **nitrosomethylurethane**,⁵ **N-nitroso-β-methylaminoisobutyl methyl ketone**,⁶ **p-tolylsulfonylethylmethyl nitrosamide**,³ and **N-nitroso-N-methyl-N'-nitroguanidine**.^{7 8}

4. Merits of Preparation

The great advantages of the present method are the availability, moderate cost, and high stability of the nitrosamide, and the suitability for large-scale preparations. The procedure is rapid and simple, and the yields are consistently higher than in any other method tried by the submitters.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 231
- Org. Syn. Coll. Vol. 5, 877
- Org. Syn. Coll. Vol. 5, 1099
- Org. Syn. Coll. Vol. 6, 386
- Org. Syn. Coll. Vol. 6, 432
- Org. Syn. Coll. Vol. 6, 613
- Org. Syn. Coll. Vol. 7, 438
- Org. Syn. Coll. Vol. 8, 612

References and Notes

1. Department of Chemistry, University of Delaware, Newark, Del.
 2. F. Arndt, *Org. Syntheses*, Coll. Vol. 2, 165 (1943).
 3. Th. J. De Boer and H. J. Backer, *Org. Syntheses*, Coll. Vol. 4, 250 (1963).
 4. C. D. Gutsche, *Org. Reactions*, 8, 391–394 (1954).
 5. W. D. McPhee and E. Klingsberg, *Org. Syntheses*, Coll. Vol. 3, 119 (1955).
 6. C. E. Redemann, F. O. Rice, R. Roberts, and H. P. Ward, *Org. Syntheses*, Coll. Vol. 3, 244 (1955).
 7. A. F. McKay, *J. Am. Chem. Soc.*, **70**, 1974 (1948);
 8. A. F. McKay et al., *Can. J. Research*, **28B**, 683 (1950).
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Appendix

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

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

potassium hydroxide,
potassium hydroxide pellets (1310-58-3)

Diazomethane,
Methane, diazo- (334-88-3)

Nitrosomethylurea

Nitrosomethylurethane

N-Nitroso- β -methylaminoisobutyl methyl ketone (16339-21-2)

N-nitroso-N-methyl-N'-nitroguanidine (674-81-7)

N,N'-dimethyl-N,N'-dinitrosoterephthalamide

diethylene glycol monoethyl ether,
2-(2-ethoxyethoxy)ethanol (111-90-0)

disodium terephthalate (15596-76-6)

p-Tolylsulfonylmethylnitrosamide