



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.

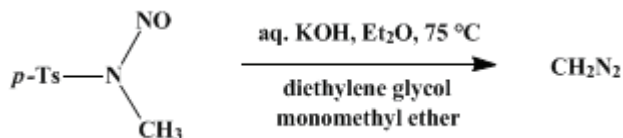
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Coll. Vol. 4, p.250 (1963); Vol. 36, p.16 (1956).

DIAZOMETHANE

[Methane, diazo-]



Submitted by Th. J. de Boer and H. J. Backer¹.

Checked by James Cason, Max J. Kalm, and R. F. Porter.

1. Procedure

Caution! Diazomethane is toxic and prone to cause development of specific sensitivity; in addition, it is potentially explosive. Hence one should wear heavy gloves and goggles while performing this experiment and should work behind a safety screen or a hood door with safety glass. Also, it is recommended that ground joints and sharp surfaces 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 take place 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 present procedure is particularly good because at no time is much diazomethane present in the distilling flask.

The hazards associated with diazomethane have been discussed by Gutsche,³ and LeWinn⁴ has reported on a fatal case of diazomethane poisoning.

A 125-ml. distilling flask is fitted with a condenser set for distillation and with a long-stem dropping funnel. The condenser is connected by means of an adapter to a 250-ml. Erlenmeyer flask. Through a second hole in the stopper of the Erlenmeyer flask is placed an outlet tube bent so as to pass into and nearly to the bottom of a second Erlenmeyer flask which is not stoppered. Both receivers are cooled in an ice-salt mixture; in the first is placed 10 ml. of ether (Note 1), and in the second 35 ml. of

ether. The inlet tube passes below the surface of the ether in the second flask.

In the distilling flask are placed a solution of 6 g. of potassium hydroxide dissolved in 10 ml. of water, 35 ml. of Carbitol (Note 2), 10 ml. of ether (Note 1), and the "Teflon"-coated bar of a magnetic stirrer (Note 3). The dropping funnel is attached and adjusted so that the stem is just above the surface of the solution in the distilling flask. There is placed in the dropping funnel a solution of 21.5 g. (0.1 mole) of *p*-tolylsulfonylethylmethyl nitrosamide (p.943) in 125 ml. of ether (Note 4). The distilling flask is heated in a water bath (Note 3) at 70–75°, the stirrer is started, and the nitrosamide solution is added at a regular rate during 15–20 minutes. As soon as all the nitrosamide solution has been added, additional ether (Note 1) is placed in the dropping funnel and added at the previous rate until the distillate is colorless. Usually 50–100 ml. additional of ether is required. The distillate contains 2.7–2.9 g. (64–69%) of diazomethane, as determined by titration² (Note 5) and (Note 6).

2. Notes

1. If an alcohol-free solution of diazomethane is required, absolute ether should be used throughout this preparation.
2. The Carbitol (monoethyl ether of diethylene glycol) was the Carbide and Carbon Chemicals Company product, which was distilled before use, b.p. 192–196°. It is a suitable solvent to render the reactants mutually soluble. Aqueous alkali with an ether solution of the nitrosamide does not yield diazomethane.
3. The same results may be obtained by an occasional careful agitation of the flask by hand; however, an explosion during this agitation by hand would be unfortunate. If the flask is placed in contact with the bottom of a beaker containing the heated water, and the magnetic stirring unit is placed in contact with the beaker, the bar may be spun satisfactorily. The checkers used the magnetic stirring apparatus, no. 9235-R, supplied by the A. H. Thomas Company, Philadelphia, Pa., and heated the water bath with the thermostated electric immersion heater, "Chill Chaser," model S-1005, supplied by the Still-Man Company, New York 56, N. Y. Satisfactory results should also be obtained by use of a combined heater and magnetic stirrer, such as no. 25210T supplied by the Will Corporation, New York 12, N. Y.
4. Nitrosamide prepared as described (p. 943), not recrystallized, is suitable for the present preparation. The solubility of the nitrosamide in ether drops sharply with temperature; below 20°, more than the specified amount of ether may be required, especially if recrystallized nitrosamide is used.
5. If an entirely dry solution of diazomethane is required, round pellets of potassium hydroxide should be used.²
6. The submitters reported that, in cases where the presence of alcohol in diazomethane solutions is not objectionable, they utilized ethanol as the solvent for the reaction mixture in which the diazomethane was prepared. They believe that ethanol has an advantage over Carbitol in that mixing of the reactants is achieved readily during the distillation, since the mixture is not viscous (see *Caution*). They used the same apparatus as described in the present procedure with the following exceptions: (1) the reaction flask was of 200-ml. capacity, (2) the first receiver was an empty 500-ml. Erlenmeyer flask, and the second flask of 100-ml. capacity contained 40 ml. of ether, and (3) a magnetic stirrer was not employed. In the reaction flask was placed a solution of 10 g. of potassium hydroxide in 15 ml. of water and 50 ml. of 95% ethanol. The water bath was heated to 60–65° and a solution of 43 g. (0.2 mole) of *p*-tolylsulfonylethylmethyl nitrosamide (p.943) in 200 ml. of ether was added from the dropping funnel in 45 minutes. After all had been added, ether (about 30 ml.) was introduced through the dropping funnel until the condensing ether became colorless. The combined solutions in the receivers contained 5.9–6.1 g. (70–73%) of diazomethane.

3. Discussion

The more important methods of preparation of diazomethane include those from nitrosomethylurea,² nitrosomethylurethan,⁵ *N*-nitroso- β -methylaminoisobutyl methyl ketone,⁶ and 1-methyl-1-nitroso-3-nitroguanidine.^{7,8} It also has been prepared from *N*-nitrosoacetamide,⁹ from *N,N'*-dimethyl-*N,N'*-dinitrosoamide and methylamine¹⁰ or other alkaline reagents,¹¹ from nitrosyl chloride and methylamine,¹² from the reaction of bis-(*N*-methyl-*N*-nitroso) terephthalamide with alkali,¹³ and by treatment of the sodium salt of formaldehyde oxime with chloramine.¹⁴

The advantage of the present method¹⁵ resides in the stability of the starting material and the manipulative advantage resulting from its solubility in organic solvents.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 4, 78
- Org. Syn. Coll. Vol. 4, 221
- Org. Syn. Coll. Vol. 4, 943
- Org. Syn. Coll. Vol. 5, 231
- Org. Syn. Coll. Vol. 5, 351
- 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, 576
- Org. Syn. Coll. Vol. 6, 613
- Org. Syn. Coll. Vol. 8, 196

References and Notes

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3. Gutsche, *Org. Reactions*, **8**, 391 (1954).
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5. *Org. Syntheses Coll. Vol. 3*, 119 (1955).
6. *Org. Syntheses Coll. Vol. 3*, 244 (1955).
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8. McKay, Ott, Taylor, Buchanan, and Crooker, *Can. J. Research*, **28B**, 683 (1950).
9. Heyns and Woyrsch, *Chem. Ber.*, **86**, 76 (1953).
10. Fawcett (to E. I. du Pont de Nemours and Co.), U. S. pat. 2,675,378 [*C. A.*, **49**, 1777 (1955)].
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13. *Org. Syntheses*, **41**, 16 (1961).
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Appendix

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

Carbitol

ethanol (64-17-5)

ether (60-29-7)

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

methylamine (74-89-5)

nitrosyl chloride (2696-92-6)

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

Nitrosomethylurea

nitrosomethylurethan

chloramine (10599-90-3)

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

1-methyl-1-nitroso-3-nitroguanidine (674-81-7)

N-nitrosoacetamide

bis-(N-methyl-N-nitroso) terephthalamide

monoethyl ether of diethylene glycol (111-90-0)

p-Tolylsulfonylmethylnitrosamide

sodium salt of formaldehyde oxime

N,N'-dimethyl-N,N'-dinitrosooxamide