



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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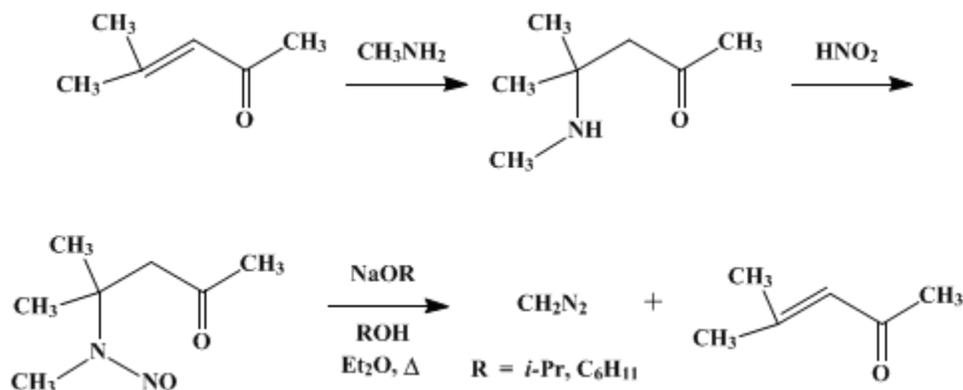
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 3, p.244 (1955); Vol. 25, p.28 (1945).*

## DIAZOMETHANE

### [Methane, diazo-]



Submitted by C. Ernst Redemann, F. O. Rice, R. Roberts, and H. P. Ward.  
 Checked by Nathan L. Drake, Charles M. Eaker, Robert K. Preston, and W. Mayo Smith.

### 1. Procedure

A. *N-Nitroso-β-methylaminoisobutyl methyl ketone*. In a 2-l. three-necked flask, fitted with a mechanical stirrer, a thermometer, and a dropping funnel, is placed 250 ml. (2.1 moles) of 30% aqueous methylamine (Note 1). The flask is surrounded by an ice bath, and the stirrer is started. When the temperature of the solution has dropped to 5°, 196 g. (2 moles) of mesityl oxide is added through the dropping funnel at such a rate that the temperature remains below 20° (Note 2) and (Note 3). After the mesityl oxide has been added, the mixture is allowed to stand without cooling for 30 minutes.

The solution is then cooled to 10° by means of the ice bath, and 125 ml. of glacial acetic acid is added through the dropping funnel at such a rate that the temperature remains below 15°; then an additional 75 ml. of the acid is added rapidly.

The ice bath is removed, and 300 ml. of 8 N sodium nitrite (Note 4) is added in 20–30 minutes to the stirred solution, which is kept at 25–35° by intermittent cooling with the ice bath. Stirring is then discontinued, and the mixture is allowed to stand for 6 hours or longer (Note 5).

The oily layer is separated from the aqueous layer, the aqueous layer is extracted with two 200-ml. portions of ether, and the combined extracts and oil are dried over calcium chloride. The drying agent is removed by filtration, and the ether is distilled on a water bath; finally, all low-boiling material is removed from the mixture on a boiling water bath under the lowest pressure obtainable with a water pump (Note 6). The nitrosoaminoketone which remains in the flask is sufficiently pure for the preparation of diazomethane (Note 7). The yield is 221–257 g. (70–80% based on mesityl oxide).

If a purer product is desired for other purposes, the nitrosoaminoketone is distilled at low pressure (see Caution). The substance boils at 119°/5 mm., at 111°/3 mm., or at 101°/1.5 mm.

*Caution! Only a small quantity of the nitrosoaminoketone should be distilled at a time. It is reported that the substance occasionally undergoes violent decomposition. If the distillation is carried out, the operator should be protected by a suitable screen or plate of safety glass (Note 8).*

B. *Diazomethane. Sodium isopropoxide method* (Note 9).

*Caution! Diazomethane is very toxic; its preparation should be carried out only in a well-ventilated hood. Individuals differ in their susceptibility; some develop symptoms similar to asthma from very*

*small concentrations, whereas others notice no ill effects from much larger quantities. The use of a safety screen is also recommended.*

Thirty milliliters of a solution of **sodium isopropoxide**, prepared from 1 g. of **sodium** and 100 ml. of **isopropyl alcohol**, is placed in a 250-ml. Claisen flask arranged for heating in a water bath. The flask is provided with a dropping funnel, a condenser, and a receiver cooled in a Dry Ice bath; this receiver is connected to a second one containing 20 ml. of anhydrous **ether**; the inlet tube of the second receiver should dip below the surface of the **ether**.

The water bath is heated to 70–75°, and one-half of a solution prepared by dissolving 15.8 g. (0.1 mole) of **N-nitroso-β-methylaminoisobutyl methyl ketone** in a mixture of 80 ml. of anhydrous **ether** and 12 ml. of **isopropyl alcohol** is added through the dropping funnel at a rate slightly greater than that of distillation. When the separatory funnel is empty, an additional 15 ml. of the solution of **sodium isopropoxide** is added; the remainder of the solution of nitroso compound is then added as before. Anhydrous **ether** is then added gradually through the dropping funnel until the condensing **ether** becomes colorless. The **diazomethane** comes over with the **ether** as a golden yellow distillate. The process can be continued until all the nitrosoaminoketone has been decomposed. The yield of **diazomethane**, which varies with the purity of the nitrosoaminoketone, is 1.9–2.5 g (45–60%).

C. **Diazomethane. Sodium cyclohexoxide method (Note 10).** A solution of sodium cyclohexoxide is prepared from 4 g. of **sodium** and 100 ml. of **cyclohexanol (Note 11)** in a 2-l. flask; the **cyclohexanol** is heated to boiling under reflux to speed up the formation of the alkoxide. As soon as the **sodium** has disappeared, heating is discontinued and the condenser is removed. When solid begins to separate from the solution, the mixture is stirred with a stout rod to prevent the formation of a hard cake. The flask is surrounded by an ice bath, and, when the temperature of the mixture has dropped to 10°, 300 ml. of dry **ether** and a solution of 49 g. (0.33 mole) of **N-nitroso-β-methylaminoisobutyl methyl ketone** dissolved in 600 ml. of dry **ether** are added. The flask is connected to a 25-cm. fractionating column and an efficient water-cooled condenser (**Note 12**). The delivery end of the condenser should be connected to an adapter which dips below the surface of 50 ml. of **ether** contained in a 1-l. Erlenmeyer flask immersed in an ice bath. The mixture is heated by a water bath whose temperature is maintained at 50–55°. Distillation is continued until the condensing **ether** is colorless; usually 700–750 ml. of distillate containing 10–11 g. (77–84% yield) (**Note 13**) of **diazomethane** is collected (**Note 14**) and (**Note 15**). The **diazomethane-ether** solution may be purified further with only slight loss by drying over **potassium hydroxide** pellets (**Note 16**) and redistillation through a fractionating column.

## 2. Notes

1. **Methylamine** is available from several manufacturers. The Commercial Solvents Corporation and Rohm and Haas Company offer an aqueous solution containing 30% to 33% of amine. Solutions of other strengths are satisfactory if appropriate quantities are employed. The amine solution may be prepared from the hydrochloride by adding slowly 210 ml. of 10 *N* **sodium hydroxide** solution to an ice-cold solution of 142 g. (2.1 moles) of **methylamine hydrochloride** in 250 ml. of water. The resulting solution is used without further treatment.
2. The **mesityl oxide** should be freshly distilled.
3. The length of time needed for this addition varies with the efficiency of the cooling bath; a period of 30 minutes to 1 hour is usually required.
4. The nitrite solution is very nearly saturated. The **sodium nitrite** need not be of c.p. grade; if it is less pure, appropriate allowance must be made when the solution is prepared.
5. It is preferable to allow the mixture to stand overnight; care should be taken, however, that its temperature does not exceed 35° at any time.
6. The pressure should not be above 30 mm.; a pressure of 20 mm. is desirable.
7. Because of the low cost of the starting materials and the stability in storage of the nitrosoaminoketone, this substance is an excellent intermediate for preparing **diazomethane**. One of the submitters (Redemann) reports that a sample of the crude material was kept in the laboratory in a brown bottle for more than 2 years without evident decomposition; the trace of **acetic acid** remaining in the ketone tends to stabilize it.
8. One of the submitters (Redemann) reports that he has never experienced difficulty during distillation

of this ketone.

9. Submitted by F. O. Rice, R. Roberts, and H. P. Ward.

10. Submitted by C. Ernst Redemann.

11. The [cyclohexanol](#) may be replaced by [benzyl alcohol](#). [Benzyl alcohol](#) is reported to give a slightly increased rate of formation of [diazomethane](#) and a slightly more concentrated ethereal solution; however, the over-all yield is somewhat lower. If only a small amount of [diazomethane](#) is wanted, concentrated aqueous [sodium hydroxide](#) may replace the solution of the alkoxide of [cyclohexanol](#). The yield under these conditions is 40–50%.

12. A column with smooth packing or smooth inner surface should be used; rough surfaces catalyze the decomposition of [diazomethane](#). A column helps to remove [mesityl oxide](#).

13. The [diazomethane](#) content of the ethereal solution may be determined by the method described previously.<sup>1</sup>

14. A solution of [diazomethane](#) in dry [ether](#) may be stored in a smooth flask or bottle in a refrigerator for several weeks. Since slow decomposition of the [diazomethane](#) occurs, the concentration of the solution should be checked before use.

15. Other alkyl diazo compounds can be prepared readily by the same general method with some alterations because of the lower volatility of the higher homologs.<sup>2</sup>

16. Pellets are recommended because their smooth surface causes little decomposition of [diazomethane](#).

### 3. Discussion

[Diazomethane](#) has been prepared from [nitrosomethylurea](#),<sup>1,3</sup> from [nitrosomethylurethane](#),<sup>4,5</sup> from a mixture of [chloroform](#) and [hydrazine hydrate](#) by reaction with [potassium hydroxide](#),<sup>6</sup> and from [N-methyl-N-nitroso-N'-nitroguanidine](#) with [potassium hydroxide](#).<sup>7</sup> The methods described above are adapted from the work of Kenner.<sup>8,9</sup> Two reviews of the reactions and use of [diazomethane](#) have appeared.<sup>10,11</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 3, 119](#)
- [Org. Syn. Coll. Vol. 4, 250](#)
- [Org. Syn. Coll. Vol. 5, 351](#)

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### References and Notes

1. [Org. Syntheses Coll. Vol. 2, 165 \(1943\)](#).
2. Adamson and Kenner, *J. Chem. Soc.*, **1937**, 1551.
3. Owen, *Current Sci. India*, **12**, 228 (1943).
4. von Pechmann, *Ber.*, **27**, 1888 (1894); **28**, 855 (1895).
5. Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).
6. Staudinger and Kupfer, *Ber.*, **45**, 505 (1912).
7. McKay, *J. Am. Chem. Soc.*, **70**, 1974 (1948).
8. Jones and Kenner, *J. Chem. Soc.*, **1933**, 363.
9. Adamson and Kenner, *J. Chem. Soc.*, **1935**, 286; **1937**, 1551.
10. Smith, *Chem. Revs.*, **23**, 193 (1938).
11. Eistert, *Angew. Chem.*, **54**, 99, 124 (1941).

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### Appendix

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

sodium cyclohexoxide

calcium chloride (10043-52-4)

acetic acid (64-19-7)

ether (60-29-7)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

Cyclohexanol (108-93-0)

sodium nitrite (7632-00-0)

potassium hydroxide (1310-58-3)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium isopropoxide (683-60-3)

Benzyl alcohol (100-51-6)

Mesityl oxide (141-79-7)

hydrazine hydrate (7803-57-8)

Methylamine hydrochloride (593-51-1)

methylamine (74-89-5)

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

Nitrosomethylurea

Nitrosomethylurethane

N-Nitroso- $\beta$ -methylaminoisobutyl methyl ketone (16339-21-2)

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