



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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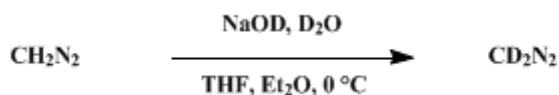
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 6, p.432 (1988); Vol. 53, p.38 (1973).*

## DIDEUTERIODIAZOMETHANE

[Methane- $d_2$ , diazo-]



Submitted by P. G. Gassman<sup>1</sup> and W. J. Greenlee.  
Checked by David G. Melillo and Herbert O. House.

### 1. Procedure

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

A distilled, ethereal solution (300 ml.) containing approximately 0.06 mole of [diazomethane](#) (Note 1) is prepared from 22.5 g. of a 70% dispersion (15.8 g., 0.063 mole) of [bis-\(\*N\*-methyl-\*N\*-nitroso\)terephthalamide](#) (Note 2), 75 ml. of aqueous 30% [sodium hydroxide](#), 55 ml. of [diethylene glycol monoethyl ether](#), and 375 ml. of [diethyl ether](#) by the procedure described in *Org. Synth., Coll. Vol. 5, 351 (1973)*. The receiving flask containing the ethereal [diazomethane](#) is capped with a rubber stopper fitted with a drying tube containing potassium hydroxide pellets to protect the solution from atmospheric moisture. The concentration of [diazomethane](#) may be determined either by titration with ethereal [benzoic acid](#) (Note 3) or spectrophotometrically (Note 4).

A dry, 250-ml. Erlenmeyer flask equipped with a Teflon-coated magnetic stirring bar is charged with 11 ml. of a solution (Note 5) containing 0.01 mole of [sodium deuterioxide](#) in 10 ml. of [deuterium oxide](#) and 1 ml. of anhydrous [tetrahydrofuran](#). After the solution has been cooled in an ice bath, 120 ml. of the ethereal solution containing 0.039 mole of [diazomethane](#) is added, the flask is stoppered loosely with a cork, and the reaction mixture is stirred vigorously at 0° for one hour. The lower [deuterium oxide](#) layer is removed with a pipette and a fresh 11-ml. portion of the [sodium deuterioxide](#) solution is added. This mixture is then stirred for one hour at 0°, and the process is repeated until a total of four exchanges have been performed. The ethereal [diazomethane](#) solution is then decanted into a clean, dry, 250-ml. Erlenmeyer flask and dried over 10 g. of anhydrous [sodium carbonate](#). The resulting solution (approximately 110 ml.) contains (spectrophotometric analysis, (Note 4), or titration with [benzoic acid](#), (Note 3)) 0.020–0.022 mole (51–56%) of [dideuteriodiazomethane](#), which is 98–99% deuterated (Note 6).

### 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 in *Org. Synth., Coll. Vol. 4, 250 (1963)*. As is also recommended, 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. Explosion of [diazomethane](#) has been observed at the moment crystals (sharp edges!) suddenly separated from a supersaturated solution. Stirring with a Teflon-coated magnetic stirrer is much preferred to swirling the reaction mixture by hand (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 encountered with [diazomethane](#). Particular caution should be exercised when an organic solvent boiling higher than [ether](#) is used. Because such a solvent has a vapor pressure lower than [ether](#), the concentration of [diazomethane](#) in the vapor above the reaction mixture is

greater and an explosion is more apt to occur. Since most **diazomethane** explosions occur during distillation, procedures that avoid distillation offer certain advantages. An **ether** solution of **diazomethane** satisfactory for many uses can be prepared as described in *Org. Synth.*, **Coll. Vol. 2**, 165 (1943), 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!). However, the reported potent carcinogenicity<sup>2</sup> of **nitrosomethylurea** mitigates other advantages of this procedure. Two procedures involving distillation of **diazomethane**, those in *Org. Synth.*, **Coll. Vol. 4**, 250 (1963) and **Coll. Vol. 5**, 351 (1973), may be recommended. In neither case is there much **diazomethane** present in the distilling flask. The hazards associated with **diazomethane** are discussed by Gutsche.<sup>3</sup>

2. The submitters used an undistilled ethereal solution of **diazomethane**, prepared from **nitrosomethylurea** (Note 1).<sup>4</sup> For use in the hydrogen–deuterium exchange reaction described, ethereal **diazomethane** solutions prepared by any standard preparative procedures (Note 1) appear to be equally satisfactory: [*Org. Synth.*, **Coll. Vol. 4**, 250 (1963), **Coll. Vol. 2**, 165 (1943), and **Coll. Vol. 5**, 351 (1973)].

3. The concentration of **diazomethane** may be determined by reaction of an aliquot of the ethereal solution with a weighed excess of **benzoic acid** in cold (0°) **ether** solution, as described in *Org. Synth.*, **Coll. Vol. 2**, 165 (1943). The unchanged **benzoic acid** is then determined by titration with standard aqueous 0.1 M **potassium hydroxide**.

4. *Caution! The following spectrophotometric analysis should be performed in a hood.* To determine the concentration of **diazomethane** obtained in this preparation, a 5-ml. aliquot of the distilled solution is diluted to 25 ml. with **ether**, and a portion of this solution is placed in a cylindrical Pyrex cell with an internal diameter of 1.0 cm. The optical density of the solution is determined at 410 nm with a suitable colorimeter such as a Bausch and Lomb Spectronic 20. From the molecular extinction coefficient,  $\epsilon$  7.2, at 410 nm for **diazomethane** in **ether** solution, the concentration of **diazomethane** can be calculated. In a typical preparation the optical density of the diluted solution at 410 nm was 0.46 corresponding to a **diazomethane** concentration of 0.064 M; thus, the concentration of the undiluted solution was 0.32 M, corresponding to a 77% yield of **diazomethane**.

5. It is convenient to prepare 110 ml. of this solution at a time. Since **hydrogen** is evolved, the solution should be prepared in a hood. A dry, 250-ml. three-necked flask is fitted with a magnetic stirrer, a rubber septum, a glass stopper, and a 125-ml. Erlenmeyer flask attached to the third neck of the reaction flask with a 10-cm. length of Gooch rubber tubing or nylon tubing. The apparatus is flushed with **nitrogen** from a hypodermic needle inserted through the rubber septum. Small, freshly cut chips of metallic **sodium** (2.3 g., 0.10 g.-atom) are placed in the Erlenmeyer flask and 100 ml. of **deuterium oxide** (99.7% pure grade obtained from Columbia Organic Chemicals Company, Inc.) is placed in the reaction flask. With a hypodermic needle inserted through the rubber septum to permit the escape of **hydrogen**, the **sodium** chips are added, slowly and with stirring, to the reaction vessel. When reaction with the **sodium** is complete, the solution is diluted with 10 ml. of anhydrous **tetrahydrofuran** and stored under a **nitrogen** atmosphere.

6. The **deuterium** content can be determined by reaction of the deuterated **diazomethane** with **benzoic acid-*-d*** in anhydrous **ether** followed by analysis of **methyl benzoate** for **deuterium** content either by <sup>1</sup>H NMR spectroscopy or by mass spectroscopy. **Benzoic acid-*-d*** is prepared by heating a mixture of 48.6 g. (0.216 mole) of **benzoic anhydride** (obtained from Aldrich Chemical Company, Inc.), 0.10 g. (0.00090 mole) of anhydrous **sodium carbonate**, and 7.0 g. (0.35 mole) of **deuterium oxide** to 90° for 2 hours. The resulting mixture is distilled at atmospheric pressure in a short-path still fitted with a receiver protected from atmospheric moisture by a drying tube. After removal of a forerun, b.p. 100–101°, the **benzoic acid-*O-d*** is collected at 245–247°. During the distillation it is necessary to warm the distillation apparatus with a heat gun or an IR lamp to prevent solidification of the **benzoic acid-*O-d*** before it reaches the receiver.

*Caution! The following reaction should be performed in a good hood (Note 1).* A cold (0°) solution of 1.43 g. (0.0116 mole) of **benzoic acid-*O-d*** in 10 ml. of anhydrous **ether** is placed in a dry, 100-ml., round-bottomed flask fitted with a rubber stopper and a Teflon-coated magnetic stirring bar. The flask is cooled in an ice bath, and a sufficient amount of the ethereal **dideuteriodiazomethane** solution is added from a pipette, providing excess **dideuteriodiazomethane** in the reaction mixture. The reaction flask is stoppered loosely, and the resulting yellow solution is stirred at 0° for 10 minutes and concentrated by first warming the solution on a steam bath in the hood, then removing the last traces of solvent under

reduced pressure. The residual liquid **methyl benzoate** (1.4–1.5 g., 90–95% yield) is analyzed for **deuterium** content. For a  $^1\text{H}$  NMR analysis, the spectrum of the pure liquid is taken and the extent of deuteration is determined by integration of the areas under the multiplet in the region  $\delta$  7.1–8.3 (aromatic CH) and the peak at  $\delta$  3.82 ( $\text{OCH}_3$ ). For mass spectroscopic analysis, the mass spectra of the deuterated sample and a sample of undeuterated **methyl benzoate** each are measured at an ionizing potential sufficiently low (approximately 12 eV.) to minimize the formation of an M-1 fragment at  $m/e$  135 in the spectrum of the deuterated sample. The relative abundances of the  $m/e$  136 and 137 peaks in the spectrum of the undeuterated sample are then used to correct the peaks at  $m/e$  137, 138, and 139 in the deuterated sample for contributions from the  $^{13}\text{C}$  isotope. From the relative abundances of the  $m/e$  136 peak and the corrected  $m/e$  137, 138, and 139 peaks in the spectrum of the undeuterated sample the relative proportions of  $d_0$ ,  $d_1$ ,  $d_2$ , and  $d_3$  species in the deuterated **methyl benzoate** can be calculated. Both  $^1\text{H}$  NMR and mass spectral analysis indicated the **methyl benzoate** to be 98% deuterated (6–7%  $d_2$  species and 93–94%  $d_3$  species). When the **dideuteriodiazomethane** solution was allowed to react with undeuterated **benzoic acid**, **hydrogen–deuterium** exchange occurred more rapidly than esterification. The **methyl benzoate** produced was 70% deuterated ( $^1\text{H}$  NMR analysis) and contained 4%  $d_0$ , 37%  $d_1$ , 30%  $d_2$  and 29%  $d_3$  species (mass spectral analysis).

### 3. Discussion

The exchange procedure described was developed for the preparation of **dideuteriodiazomethane**, for use in labeling studies. It is basically a modification of a procedure that has been used extensively;<sup>5</sup> however, the literature procedures give relatively little detail. This modified procedure permits the synthesis of fairly large amounts of high-purity **dideuteriodiazomethane**. **Dideuteriodiazomethane** has also been prepared from *N*-nitrosomethyl- $d_3$ -urea and related trideuterated **diazomethane** precursors.<sup>6</sup> Deuterated **chloroform** and **hydrazine hydrate** have also been used to prepare **dideuteriodiazomethane**.<sup>3,7</sup>

The procedure described provides a general method for the **hydrogen–deuterium** exchange of simple diazoalkanes.

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### References and Notes

1. Department of Chemistry, The Ohio State University, 140 West 18th Avenue, Columbus, Ohio 43210. [Present address: Department of Chemistry, University of Minnesota, 207 Pleasant Street S. E., Minneapolis, Minnesota 55455].
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7. A procedure very similar to that described in this preparation has subsequently been published: S. P. Markey and G. J. Shaw, *J. Org. Chem.*, **43**, 3414 (1978). The authors of this paper were evidently unaware of the prior publication of this *Org. Synth.* procedure [*Org. Synth.*, **53**, 38 (1973)].

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

Methane-d<sub>2</sub>, diazo-

N-nitrosomethyl-d<sub>3</sub>-urea

ether,  
diethyl ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium carbonate (497-19-8)

nitrogen (7727-37-9)

Benzoic acid (65-85-0)

Benzoic anhydride (93-97-0)

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

sodium (13966-32-0)

hydrazine hydrate (7803-57-8)

methyl benzoate (93-58-3)

Diazomethane (334-88-3)

Nitrosomethylurea

Tetrahydrofuran (109-99-9)

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

diethylene glycol monoethyl ether (111-90-0)

Dideuteriodiazomethane (14621-84-2)

sodium deuterioxide (14014-06-3)

deuterium oxide (7789-20-0)

deuterium (7782-39-0)

Benzoic acid- -d,  
benzoic acid-O-d (1005-01-2)

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