



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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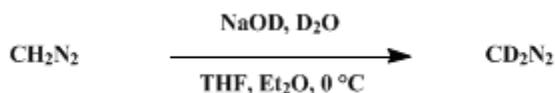
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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

DIDEUTERIODIAZOMETHANE

[Methane- d_2 , diazo-]



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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 carcinogenicity² 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.³

2. The submitters used an undistilled ethereal solution of **diazomethane**, prepared from **nitrosomethylurea** (Note 1).⁴ 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, ϵ 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 ¹H 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 ^1H 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 δ 7.1–8.3 (aromatic CH) and the peak at δ 3.82 (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}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 ^1H 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 (^1H 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;⁵ 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.⁶ Deuterated [chloroform](#) and [hydrazine hydrate](#) have also been used to prepare [dideuteriodiazomethane](#).^{3,7}

The procedure described provides a general method for the [hydrogen–deuterium](#) exchange of simple diazoalkanes.

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-d₂, diazo-

N-nitrosomethyl-d₃-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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