

**STANDARD OPERATING PROCEDURE:
DIAZOMETHANE GENERATION¹**

PI: _____	Room & Building: _____
Department: _____	Research Group: _____
Date: _____	Pertains to Lab Protocol: _____

DESCRIPTION

Diazomethane is a common methylating reagent for carboxylic acids. It has found wide application in the methylation of phenols, enols (alkenols), and heteroatoms such as nitrogen and sulfur.

PROCEDURE

Attach the experimental protocol(s) for the generation of diazomethane.

MATERIALS & HAZARDS

Influenced by the scale of production, several methods are available for the generation of diazomethane, each requiring a different suite of materials/chemicals.

Principal Materials Used (CAS No.)	Corrosive	Irritant	Sensitizer	Reproductive toxin	Acutely Toxic	Carcinogen	Flammable	Combustible	Water-Reactve	Shock-Sensitive	Pyrophoric	Oxidizer	Biotoxin	Other Comments:
Diazomethane (334-88-3)		X	X		X		X	X						See comment 1, below.
Diazald (85-11-5)		X												
MNNG (70-25-7)		X		X		X								See comment 2, below.
Ethanol (64-17-5)		X			X		X							
Potassium hydroxide (1310-58-3)	X	X												See comment 3, below.
Sodium hydroxide (1310-73-2)	X	X												See comment 3, below.
Acetone (67-64-1)		X					X							
Ether (60-29-7)		X			X		X			X				See comment 4, below.
4-methoxybenzoic acid (100-09-4)		X												
Silicic acid (7699-41-4)		X												
Carbitol (111-90-0)		X						X						

Other comments:

1. Diazomethane is extremely toxic and highly irritating, causing pulmonary edema when inhaled in high concentrations. Long-term, low-level exposure may lead to sensitization, resulting in asthma-like symptoms. Diazomethane has also been known to explode unaccountably, both as a gas and in solution. Rough surfaces are proven initiators of detonation.

2. MNNG is toxic, a severe irritant, a probably carcinogenic to humans (IARC Group 2A), and a mutagen in microorganisms, plants, animals, and cultured human cells. Prolonged or repeated contact may lead to sensitization.
3. Potassium hydroxide or sodium hydroxide contact with moisture or water may generate sufficient heat to ignite combustible materials.
4. Ether is extremely flammable. It forms explosive peroxides after prolonged exposure to light and air.

ENGINEERING/VENTILATION CONTROLS

Given diazomethane's toxicity and the possibility of explosion, all reactions involving the preparation and use of diazomethane should be performed in a chemical fume hood, behind the shatterproof sash, and behind a portable protective shield.

RECOMMENDED PERSONAL PROTECTIVE EQUIPMENT

- ✓ Protective clothing
- ✓ Gloves
 - *Incidental contact:* double-glove with 8-mil nitrile or single-glove with 15-mil or heavier nitrile
 - *For possible extended contact or spill clean-up:* Norfoil gloves (e.g., Silver Shield, 4H, or New Barrier™ brand) when transferring diazomethane in ether or when making reagent solutions containing this material
- ✓ Chemical splash goggles
- ✓ Face shield (if hood's sash is not in the down, protective position)
- ✓ Closed-toed, impervious footwear
- ✓ Consider using a portable safety shield (e.g. LAB-GUARD®) for additional protection against explosion

ADDITIONAL PRECAUTIONS

- Incompatibles: Contact between diazomethane and alkali metals, calcium sulfate (Drierite® dessicant), calcium chloride, boiling stone, or copper powder will cause explosion.
- Never proceed with this procedure using cracked glassware or equipment with sharp or rough surfaces. These conditions may cause an explosion.
- Improperly fitting joints provide a place for diazomethane to collect.
- Avoid the use of PVC tubing or other plastic tubing.

MATERIAL SAFETY DATA SHEETS

MSDSs are available electronically via EHS Department's Web page: <http://www.uos.harvard.edu/ehs/msds/>. An option, but consider collecting in a binder the MSDSs that arrive with each order.

DECONTAMINATION

All glassware involved in the generation of diazomethane should be decontaminated using the following procedure:

1. Soak glassware in a water-and-soap bath overnight.
2. Rinse glassware clean with water followed by acetone.
3. Bake dried glassware in an oven at approximately 300°C overnight.

Note: Be extra cautious not to create any scratches in the glassware during decontamination. Check for loose fittings.

WASTE

Refer to the *Laboratory Waste Guide* posted at

<http://www.uos.harvard.edu/ehs/longwood/HarvardLongwoodLabWasteGuide.pdf>

STORAGE CONDITIONS

Diazomethane should be stored under the following conditions:

- In a refrigerator (at 4°C)
- In amber glass vials
- Separated from alkali metals, calcium sulfate, calcium chloride, boiling stones, or copper powder
- Protected from shock, heat, sparks, open flames, and physical damage

Diazald should be stored under the following conditions:

- In a chemical fume hood
- At room temperature (if storing for ≤ 1 year)
 - For prolonged storage keep the material refrigerated.
- In an amber bottle
- Protected from light

MNNG should be stored under the following conditions:

- In an amber bottle
- Keep refrigerated

EMERGENCY PROCEDURES

Refer to the emergency flip chart titled "*EHS Procedures and Response Guidelines*," posted in each laboratory and found on EHS's webpage at <http://www.uos.harvard.edu/ehs/longwood/>

ATTACHMENT
PROCEDURE FOR THE GENERATION OF DIAZOMETHANE¹

Amount of Diazomethane	Diazomethane Generators	Major Materials
<1 mmol	Aldrich diazomethane-generator with System 45 compatible connection	4-methoxybenzoic acid Ether Diazald Carbitol Potassium hydroxide Silicic acid
<1 mmol	Aldrich MNNG diazomethane-generator with System 45 compatible connection	MNNG Ether Sodium hydroxide
1-50 mmol	Mini Diazald apparatus	Diazald Ethanol Potassium hydroxide
1-100 mmol	Diazald glassware set with System 45 compatible connections	<i>(same as Mini Diazald apparatus)</i>
200-300 mmol	Macro Diazald Kits ²	Diazald Potassium hydroxide Carbitol Ether Acetone

Aldrich diazomethane-generator with System 45 compatible connection

1. Add 0.3 mmol of 4-methoxybenzoic acid and 3 mL of ether to the outside tube.
2. Add 1.71 mmol of Diazald and 1 mL of carbitol to the inside tube.
3. Assemble the two parts together.
4. Place the lower part of the outer tube in an ice bath.
5. After equilibrating to the cooling bath temperature, slowly inject dropwise, through the septum, via a syringe, 1.5 mL of 37% aqueous potassium hydroxide.
6. Gently shake the apparatus by hand to ensure mixing of reactants within the inner tube, while being careful not to allow these reactants to spill into the outer tube.
7. The solution in the outer tube may become yellow in color and persist, indicating an excess of diazomethane.
8. After 50 minutes, open the apparatus. Carefully add 0.151 g of solid silicic acid to the inner tube to destroy unreacted diazomethane.

9. Evaporate the yellow ether solution in the outside tube under a gentle stream of nitrogen affording methyl 4-methoxybenoate as a white solid product.

Aldrich MNNG diazomethane-generator with System 45 compatible connection

1. Place 1mmol or less of MNNG reagent in the inside tube along with 0.5 mL of water to dissipate any heat generated.
2. Place ether (~3 mL) in the outside tube, and assemble the two parts together by tightening the 32 mm screw cap.
3. Immerse the lower part in an ice bath and inject (dropwise, very slowly to prevent frothing or possible build-up of back pressure) about 0.6 mL of 5N sodium hydroxide through the PTFE-faced silicone septum via a syringe with a narrow gauge needle to prevent diazomethane leakage around the shank.
4. The addition of the alkali to MNNG must be done very slowly (dropwise) to prevent the mixture from getting too hot and to control the volume of gas produced.
5. The diazomethane collects in the ether, ready for use.
6. Some important points concerning the MNNG generator include:
 - a. A small needle (22-gauge or smaller) is imperative to prevent diazomethane escape.
 - b. The septum must be changed frequently, preferably each time.
 - c. The base solution must be added no faster than one drop/five seconds to avoid excessive pressure build-up.
 - d. At least 45 minutes must elapse following base injection to assure an acceptable yield (over 50%) of diazomethane.
 - e. It is best to dissolve the substrate in the ether contained in the outer tube prior to diazomethane generation so that the reagent is consumed as it is formed, in which case the intensity of the yellow color of diazomethane/ether solution may be reduced.

Mini Diazald apparatus

1. Assemble the Aldrich Mini Diazald Apparatus.
2. Fill the condenser with dry ice and then add isopropanol slowly until the cold-finger is about one-third full.
3. Add 10 ml of 95% ethanol to a solution of potassium hydroxide (5 g) in water (8 ml) in the reaction vessel.
4. Attach a 100 ml receiving flask (with Clear-Seal joint) to the condenser and cool the receiver in the dry ice/ethanol bath.
5. Provide an ether trap at the side-arm (the glass tube must have flame-polished ends). The trap should be cooled in a dry ice/acetone bath.
6. Place a separatory funnel (with Clear-Seal joint) over the reaction vessel and charge the funnel with a solution of diazald (5.0 g, 23 mmol) in ether (45 ml).

7. Warm the reaction vessel to 65°C with a water bath and add the Diazald solution over a period of one hour. The rate of distillation should approximate the rate of addition.
8. Replenish the cold finger with dry ice, as necessary.
9. When all the Diazald has been used up, slowly add 10 ml of ether and continue the distillation until the distillate is colorless. If the distillate is still yellow, add another 10 ml of ether and continue the distillation.

Diazald glassware set with System 45 compatible connections

(The method of diazomethane generation is essentially a scale-up of the procedure outlined for the Mini Diazald Apparatus)

Macro Diazald Kits²

1. Place in a three-neck flask (500 mL) a solution of 18 g (0.32 mol) of potassium hydroxide in 30 mL of water, 105 mL of Carbitol (diethylene glycol monoethyl ether) and 30 mL of ether.
2. Fill the pocket condenser with dry ice and acetone.
3. In the separatory funnel (500 mL), place a solution of 64.2 g (0.3 mol) of Diazald in 375 mL of ether.
4. Connect a 500-mL Erlenmeyer flask immersed in ice-water to the ground-glass joint of the condenser.
5. Heat the water bath to 60°C, start the magnetic stirring, and introduce the solution of the Diazald at such a rate that all the yellow vapors evolved are completely condensed in the reflux condenser with the stopcock closed.
6. Open the stopcock. The first portions of the yellow condensate fill the overflow trap which allows the liquid to follow into the receiver but prevents the undesirable passage of uncondensed vapors past the receiver.
7. Gradually raise the temperature of the water bath to 70 – 80°C until all the Diazald solution is used up and the condensate in the dry ice condenser is colorless (ether).
8. With proper replenishing of the dry ice in the condenser (about 2 kg are needed for 0.3 mol of diazomethane), a practically quantitative recovery of diazomethane and ether is achieved within 90 – 100 minutes.

Reference:

¹ Sigma Aldrich, 2003, “AL-180: Diazald, MNNG and Diazomethane Generators.”

<http://www.sigmaaldrich.com/aldrich/bulletin/AL-180.pdf>

² Hudlicky, M. An Improved Apparatus for the Laboratory Preparation of Diazomethane. *J. Org. Chem.* 1980, 45, 5377.