STANDARD OPERATING PROCEDURE:
DIAZOMETHANE GENERATION[1]

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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

Please see the attached experimental protocol 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-Reactive	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	X											
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.

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. Potassium hydroxide contact with moisture or water may generate sufficient heat to ignite combustible materials.
3. Ether is extremely flammable. It forms explosive peroxides after prolonged exposure to light and air. Please test your ether for peroxides prior to distillation as this can concentrate them and create a separate explosion hazard.

ENGINEERING/VENTILATION CONTROLS

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

RECOMMENDED PERSONAL PROTECTIVE EQUIPMENT

It is important to wear appropriate personal protective equipment, including goggles and a face shield, when working with diazomethane:

- ✓ 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
- ✓ Use a portable safety shield 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.** This includes scratched glassware such as pipettes, ground glass stoppers, etc. 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.uiowa.edu/~hpo/waste/msds.htm.

DECONTAMINATION AND HAZARDOUS WASTE COLLECTION

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

1. Collect all glassware cleaning rinsate and don't put down the drain where the material may react with metals in the piping.
2. Soak glassware in a water-and-soap bath overnight.
3. Rinse glassware clean with water followed by acetone.
4. Bake dried glassware in an oven at approximately 300°C overnight.
5. Destroy any excess diazomethane in the collected rinsate by adding an excess of acetic acid.

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

STORAGE CONDITIONS

Diazomethane should be stored under the following conditions:

- In a refrigerator (at 4°C) in a Styrofoam or plastic container that has individual slots for each vial to minimize shock. Closely inspect each container of the diazo solution before opening, looking for crystal formation around the cap (since ether can vaporize so readily, it is possible for the solution to concentrate while in storage).
- 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

ATTACHMENT

PROCEDURE FOR THE GENERATION OF DIAZOMETHANE[1]

Amount of Diazomethane	Diazomethane Generators	Major Materials
1-50 mmol	Mini Diazald apparatus	Diazald Ethanol Potassium hydroxide

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. Do not exceed the recommended distillation temperature to minimize hazards!
9. Replenish the cold finger with dry ice, as necessary.
10. 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.

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.