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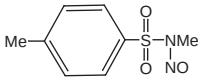
Diazald® and Diazomethane Generators

WARNING!
Because of the highly toxic and explosive nature of diazomethane, all reactions involving its preparation and use should be carried out in an efficient chemical fume hood and behind a safety shield. Avoid use of PVC tubing or other plastic tubings with Diazald® kits.

I. DIAZALD®

Diazald® (*N*-methyl-*N*-nitroso-*p*-toluenesulfonamide) is the reagent of choice for the preparation of diazomethane in quantities greater than one millimole.

1. Properties



Molecular formula	$C_8H_{10}N_2O_3S$
Formula weight	214.24
m.p.	61-62 °C
Appearance	yellow powder
Cat. No.	D2,800-0
Fieser	1, 191, 2, 102
Merck Index	139621
RTECS#	XT5950000

2. Toxicity, storage, and stability

Diazald® is a severe skin irritant and all skin contact should be avoided. The material should be stored in a brown bottle at room temperature. It is stable at room temperature for at least one year;[1] however, we recommend that the material be kept refrigerated for prolonged storage.

II. DIAZOMETHANE

1. Properties and application

Diazomethane (CH_2N_2) is a gas at room temperature, liquifies at -23 °C (density 1.45), and freezes at -145 °C. It is the most common methylating reagent for carboxylic acids and has found wide application in the methylation of phenols, enols, and heteroatoms such as nitrogen and sulfur. The preparation and reactions of diazomethane have been reviewed.[5-7]

2. Toxicity and hazards

Although diazomethane can be handled safely as a dilute solution in an inert solvent, it presents several safety hazards. It is extremely toxic[8] and highly irritating,[9] causing pulmonary edema when inhaled in high concentrations. Long-term, low-level exposure may lead to sensitization, resulting in asthma-like symptoms.[10] In addition, diazomethane has been cited as a carcinogen.[9-11]

Diazomethane has been known to explode unaccountably, both as a gas and in solution. Rough surfaces are proven initiators of detonations. De Boer and Backer[12] reported that an explosion of diazomethane had been observed at the moment of crystal formation from a supersaturated solution.

Dioxane and other solvents that may freeze should not be used as the sharp edges of crystals formed may cause an explosion.

Table I	Aldrich Diazomethane Generators	
Cat. No.	**Description**	**Amount of Diazomethane (mmol)**
Z411736	Diazomethane Generator with System 45® connection	<1
Z108898	Mini Diazald® Apparatus with Clear-Seal® joints	1-50
Z419761	Diazald® Glassware Set with System 45® connections	1-100
Z108510	Macro Diazald® Kit with Clear-Seal® joints	200-300

Table II	Contents of Deutero-Diazald® Prep Set	
Cat. No.	**Reagent**	**Quantity (g)**
D28000	Diazald®	30
164488	Sodium deuteroxide, 30wt % solution in D_2O	20
164496	2-(2-Ethoxyethoxy)ethan(ol-*d*), 97 atom % D	50
151882	Deuterium oxide, 99.9 atom % D	25

Table III	Ratios of Reagents to Diazomethane-d_2			
Diazald® (g)	**2(2-Ethoxyethoxy)(ethan(ol-*d*)) (g)**	**30% NaOD (g)**	**CD_2N_2 (mmol) produced**	**Atom % D**
5.0	50	20	12	97
10.0	50	20	24	93
15.0	50	20	36	92
20.0	50	20	48	88
21.4	50	20	50	87

III. DIAZOMETHANE GENERATORS

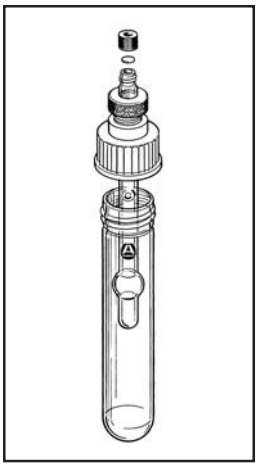


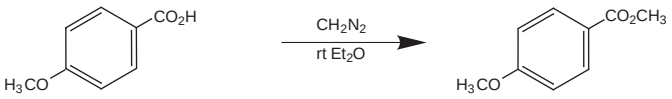
Fig. 1 Apparatus for preparing diazomethane (cooling bath not shown).

Aldrich carries several apparatuses for the preparation of diazomethane from Diazald® (see Table I on page 5). These apparatuses feature Clear-Seal® joints or System 45® connections.

1. The Aldrich Diazomethane Generator with System 45® connection

This apparatus (Fig. 1) affects the generation of diazomethane without the need for co-distillation with ether. This apparatus is mainly used for small scale GC work and preparative analysis of samples no larger than 0.3 mmol. A representative procedure follows:

To the outside tube of the Aldrich diazomethane generation apparatus add 4-methoxybenzoic acid (0.465 g, 0.300 mmol) and ether (3.0 mL). To the inside tube add Diazald® (0.367 g, 1.71 mmol) and carbitol (1.0 mL). Assemble the two parts and place the lower part of the outer tube in an ice bath. After equilibrating to the cooling bath temperature, slowly inject drop-wise through the septum via a syringe, aqueous KOH (37%, ~1.5 mL). 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. The solution in the outer tube may become yellow in color and persist, indicating an excess of diazomethane. After 50 min, open the apparatus. Carefully add solid silicic acid (0.151 g) to the inner tube to destroy unreacted diazomethane. Evaporate the yellow ether solution in the outside tube under a gentle stream of nitrogen affording methyl 4-methoxybenoate as a white solid product (0.490 g, 98.4%). GC/MS analysis should indicate the material to be analytically pure.



98% isolated yield
(0.3 mmol scale)

2. The Aldrich Mini Diazald® Apparatus

A. Description

This unit (Fig. 2) is designed for the preparation of 1 to 50 mmol of diazomethane from Diazald® or a 25 wt. % solution of Diazald® in 2-Methoxyethyl ether (diglyme), and consists of a reaction vessel and condenser in one compact piece (with 19/22 Clear-Seal® joints). The only additional equipment needed consists of an addition funnel and receiver (both of which must have Clear-Seal® joints). The major feature of this apparatus is the "cold-finger" in place of a water-jacketed condenser. When filled with dry ice/isopropanol slush, the condenser very efficiently prevents diazomethane/ether vapor from escaping into the atmosphere. A typical experimental procedure employing this apparatus follows.

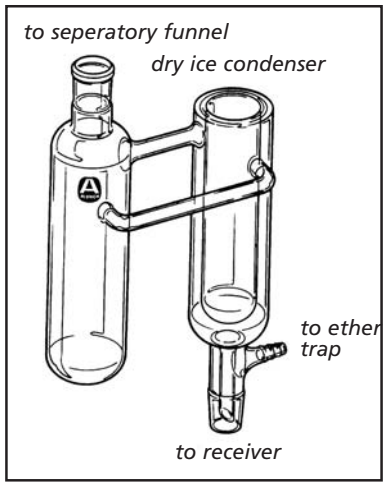


Fig. 2 Aldrich Mini Diazald® apparatus

B. Procedure

(i) For an alcohol-containing ethereal solution

Fill the condenser with dry ice, then add isopropanol slowly until the cold-finger is about one-third full. Add ethanol (95%, 10 mL) to a solution of potassium hydroxide (5 g) in water (8 mL) in the reaction vessel. Attach a 100 mL receiving flask (with Clear-Seal® joint) to the condenser and cool the receiver in dry ice/isopropanol bath. Provide an ether trap at the side-arm (the glass tube must have firepolished ends). The trap should be cooled in a dry ice/isopropanol bath.

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) or 20 mL of 25 wt. % Diazald® in diglyme (5 g, 23.3 mmol) and 30 mL of ether. Warm the reaction vessel to 65 °C with a water bath and add the Diazald® solution over a period of 20 minutes. The rate of distillation should be approximately the rate of addition. Replenish the cold-finger with dry ice as necessary. 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. The ether will contain 700 mg to 900 mg (16.6 mmol to 21.4 mmol) of diazomethane depending on whether Diazald® or Diazald® in diglyme is used respectively.

(ii) For an alcohol-free ethereal solution

If an alcohol-free ethereal solution of diazomethane is required, add 2-(2-ethoxyethoxy)ethanol (14 mL) and ether (8 mL) to a solution of potassium hydroxide (2.5 g) in water (4 mL) in the reaction vessel. Distill diazomethane as above (a similar yield is obtained).

C. Accessories for the Mini Diazald® Apparatus

Description	Cat. No.
Round-bottom flask, 50 mL	Z100331
Round-bottom flask, 100 mL	Z100358
Round-bottom flask, 250 mL	Z100366
Separatory funnel, with PTFE stopcock, 125 mL	Z100382
PTFE stopper	Z100390

Aldrich lists several sizes of separatory funnels and receivers with ⅄19/22 Clear-Seal® joints.

3. Diazald® Glassware Set with System 45® connections

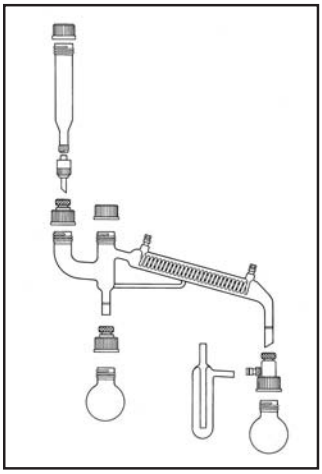


Fig. 3 Typical set-up with Diazald® Glassware Set (heating and cooling baths are not included).

A. Description and use

This glassware set (Fig. 3) incorporates System 45® connections that eliminate glass joints, clamps, and grease, and permits the safe preparation of diazomethane (~100 mmol) from Diazald®. The unique, one-piece distillation head features a highly efficient coiled condenser.

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

4. The Macro Diazald® Kit

Description	Cat. No.
Diazald® Glassware Set, complete	Z419761
Replacement parts	
Addition funnel, 60 mL, with PTFE valve	Z419850
Distillation head	Z419788
Solid-top cap, with PTFE liner, 32 mm	Z416983
Quick-disconnect fittings, with ¼ in. hose fitting	Z417432
O-rings, Viton®, size 2-011, for use with quick-disconnect fittings	Z418439

A. Description and use

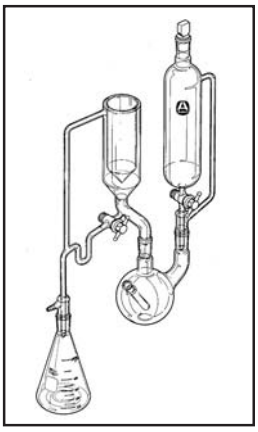


Fig. 4. Macro Diazald® Kit set-up (heating and cooling baths are not shown).

Designed by M. Hudlicky,[14] this kit (Fig. 4) enables the preparation of 200 to 300 mmol of diazomethane from Diazald®. Like the Mini Diazald® Apparatus, it features a dry ice cold-finger condenser which quantitatively condenses all the diazomethane/ether vapor. It also includes a U-tube vapor trap and PTFE stopcock to ensure trapping of all vapors. The stopcock is closed at the start of distillation. As the distillate drips off the condenser, the stopcock is opened and the first portions fill the trap, allowing the condensate to collect in the Erlenmeyer flask, but preventing the escape of uncondensed vapors into the receiver.

Hudlicky[15] has proposed a modification employing a cold trap (such as that used in vacuum systems) as the receiver vessel.

B. Replacement Parts

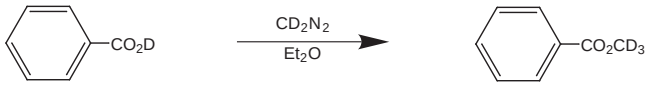
Description	Cat. No.
PTFE stopper, ST/NS 24/40	Z115584
Dropping funnel, 500 mL	Z115541
Round-bottom flask, 2-neck, 500 mL	Z115576
Cold-finger condenser assembly	Z115592
Erlenmeyer flask, 500 mL	Z115568

IV. DEUTERATED DIAZOMETHANE

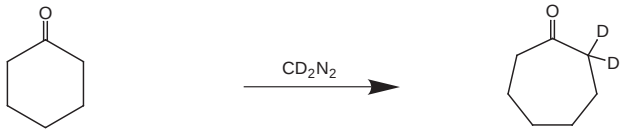
1. Applications

Diazomethane-d_2 (CD_2N_2)[16] is a useful reagent for the simple preparation of a wide variety of deuterated compounds widely used in NMR spectroscopy. Deuterated compounds are also important stereochemical and mechanistic tools in isotope effect studies and as "cold-labeled" materials for biological investigations.

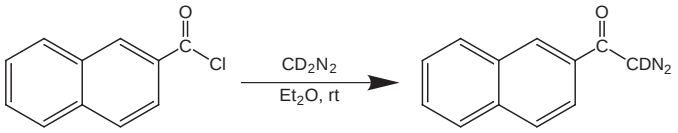
Methyl esters from carboxylic acids[17]



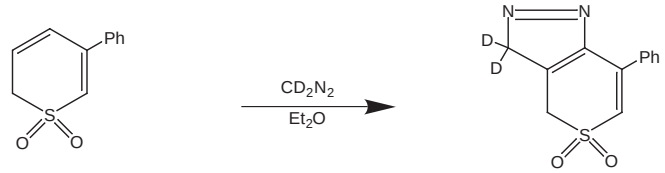
Ring expansion of ketones[18-20]



Diazoketone formation from carboxylic acid halides[21]



Pyrazoline formation[22]



2. Generation and use of diazomethane-d_2

The Diazald® Glassware Set or the Mini Diazald® Apparatus may be used. **WARNING: All safety precautions emphasized for diazomethane (Section III) apply to diazomethane-d_2 also.**

2-(2-Ethoxyethoxy)ethan(ol-*d*) (carbitol-*d*, 50 g) and anhydrous ether (20 mL) are added to a solution of 30% sodium deuteroxide in D_2O (20 g). This mixture is placed in a 250 mL distilling flask equipped with a dropping funnel, an efficient condenser, a magnetic stirring bar, and a water bath at 70 °C. The condenser is connected to two receiving flasks in series, the second of which contains 20 to 30 mL of anhydrous ether. The inlet tube of the second receiver dips below the surface of the ether and both receivers are cooled to 0 °C. The solution (occasionally a second layer forms without detriment) in the distilling flask is stirred vigorously and a solution of Diazald® in anhydrous ether (10 mL per gram of Diazald®) is added through the dropping funnel over a period of 20 minutes. When the dropping funnel is empty, anhydrous ether is added slowly until the distillate is colorless (~60 mL).

The combined ethereal distillates contain about 2.5 mmol of deuterated diazomethane per gram of Diazald® used. They also contain some HOD-D_2O. Drying over solid KOH should be avoided, as drying for 1 hour leads to ca. 15% exchange. Reaction of the wet ethereal deuterated diazomethane with a deuterated carboxylic acid (RCOOD-see Table III on page 5) gives deuterated methyl esters containing 90% of the deuterium present in the deuterated diazomethane.

Deuterated carboxylic acids (RCOOD) are prepared by washing an ethereal solution of the acid (RCOOD, 50 mmol) with four 5 g portions of deuterium oxide. The isotopic purity of the deuterated methyl ester is improved to >95% (using 97% D deuterated diazomethane) if 5 g of D_2O is added to the ethereal deuterated diazomethane solution, followed by vigorous stirring during addition of the deuterated carboxylic acid.

The quantities of 2-(2-ethoxyethoxy)ethan(ol-*d*) and 30% NaOD in D_2O supplied in the kit may be used to generate deuterated diazomethane of higher isotopic purity by using less Diazald® (see Table III on page 5).

V. DIAZOMETHANE PRECURSORS AND RELATED PRODUCTS

Description	Cat. No.
Diazald®	**D28000**
Diazald®-*N*-methyl-^{13}C, 99 atom % ^{13}C	**277614**
Diazald®-*N*-methyl-^{13}C-*N*-methyl-d_3, 99 atom % ^{13}C, 99.5 atom % D	**295981**
Diazald®-*N*-methyl-d3, 98 atom % D	**329908**

VI. REFERENCES AND NOTES

1) See a precaution published in ref. 12 below, p 945: "Although this material has been kept at room temperature for years without significant change, there has been reported one instance in which a sample stored for several months detonated spontaneously. For long periods of storage, it is recommended that the material be recrystallized and placed in a dark bottle."
2) McKay, A.F. *J. Am. Chem. Soc.* **1948**, 70, 1974.
3) *Registry of Toxic Effects of Chemical Substances;* NIOSH: Cincinnati, OH; MF4200000.
4) Mandell, J.D.; Greenberg, *J. Biochem. Biophys. Res. Commun.* **1960**, *3*, 575; Adelberg, E.A.; Mandel, M.; Chen, G.C.C. *ibid.* **1965**, *18*, 788.
5) Pizey, J.S. In *Synthetic Reactions*, Halsted: New York, **1974**; Vol. II, Chapter 4.
6) Hopps, H.B. *Aldrichimica Acta* **1970**, *3(4)*, 9.
7) Black, T.H. *Aldrichimica* **1983**, *16(1)*, 3 (reprint available on request).
8) Gutsche, C.D. In *Organic Reactions*; Adams, R., Ed.; John Wiley & Sons: New York, **1954**; Vol. VIII, p 392.
9) *Registry of Toxic Effects of Chemical Substances*; NIOSH: Cincinnati, OH; PA 7000000.
10) Lewis, C.E. *Occup. Med.* **1964**, *6*, 91.
11) Schoental, R. *Nature* **1960**, *188*, 420.
12) De Boer, T.J.; Backer, H.J. In *Organic Synthesis, Collective Volume IV*, Rabjohn, N., Ed.; John Wiley & Sons: New York, **1963**; p 250.
13) Fales, H.M.; Jaouni, T.M.; Babashak, J.F. *Anal. Chem.* **1973**, *43*, 2302. Reprinted with permission . Copyright by the American Chemical Society.
14) Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377. This reference contains experimental procedures.
15) Hudlicky, M. *J. Org. Prep. Proced. Int.* **1982**, *14*, 354.
16) Campbell, J.R. *Chem. Ind.* **1972**, 540.
17) Arndt, F. In *Organic Syntheses, Collective Volume II,* Blatt, A.H., Ed.; John Wiley & Sons: New York, **1943**; p 165.
18) De Boer, T.J.; Backer, H.J. In *Organic Syntheses, Collective Volume IV*, Rabjohn, N., Ed.; John Wiley & Sons: New York, **1963**; p 225.
19) House, H.O.; Grubbs, E.J.; Cannon, W.F. *J. Am. Chem. Soc.* **1960**, *82*, 4099.
20) Cram, D.J.; Helgersen, R.C. *J. Am. Chem. Soc.* **1966**, *88,* 3515.
21) Bachmann, W.E.; Struve, W.S. In *Organic Reactions,* Adams, R., Ed.; John Wiley & Sons: New York, **1942**; p 50.
22) Bradamante, S.; Maiorana, S.; Mangia, A.; Pazani, G. *Tetrahedron Lett.* **1969**, 2871.
23) Ngan, F.; Toofan, M., *J. Chrom. Sci.* **1991**, *29*, 8.

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