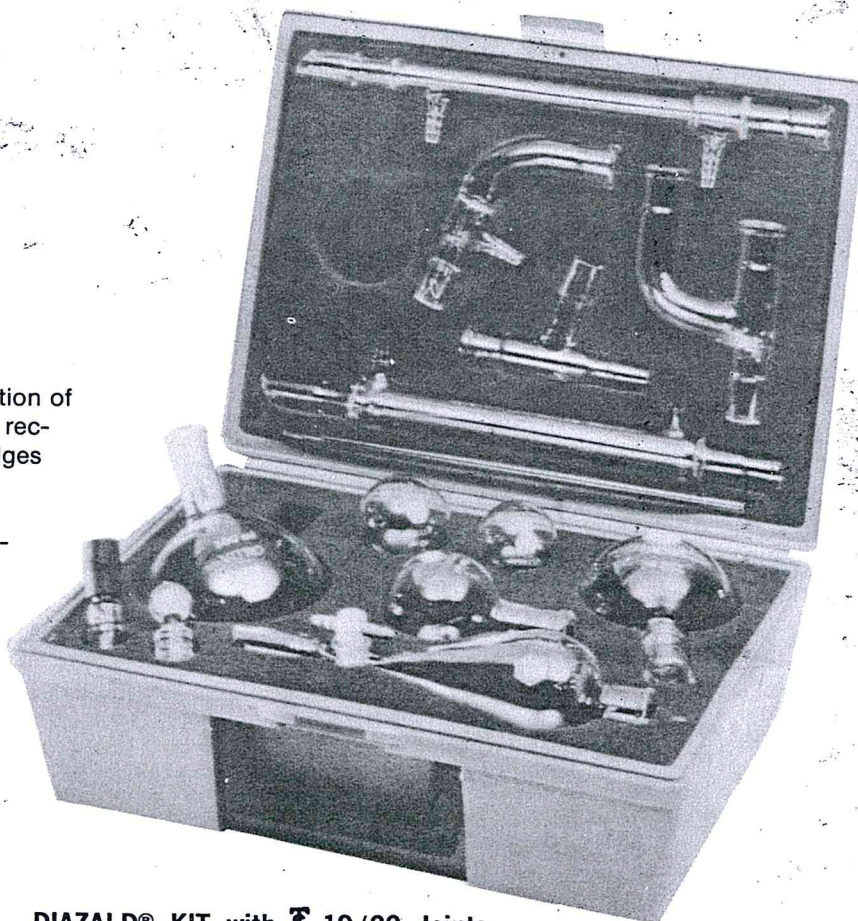


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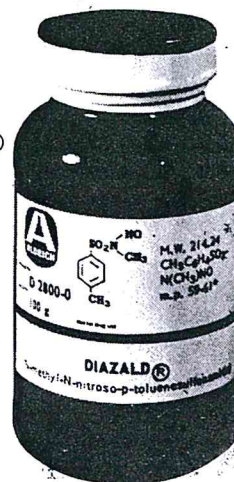
(1) T. J. de Boer and H. J. Backer, Org. Syn. Coll. Vol. 4, John Wiley and Sons, New York, N. Y. 963 p. 250.

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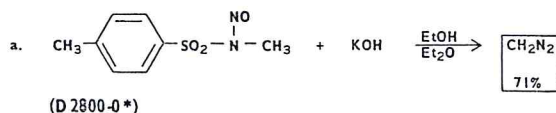
Preparation and Reactions of Diazomethane

Harvey B. Hopps, Research Division, Aldrich Chemical Company, Inc.

Diazomethane is one of the most versatile reagents available to the organic chemist. Not only does it serve as a methylene precursor but it also will produce some interesting heterocyclic systems. The aim of this review is to provide examples of some of its many applications from the synthetic point of view. Both well known examples and reactions described in the recent literature are presented. As diazomethane is both toxic and explosive, all work with it should be carried out behind a safety shield in an efficient hood. Further details of safety in the preparation and handling of diazomethane are included in the discussions of de Boer and Backer¹ and Moore and Reed.² Aldrich has always been interested in reagents used to prepare diazomethane. Our first precursor offered for sale in 1951 was N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), one of the reagents listed below.

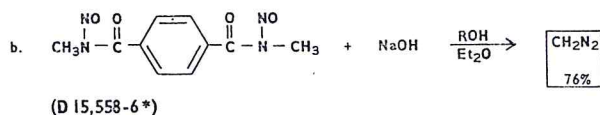
PREPARATION OF DIAZOMETHANE

The reaction of Diazald® (N-methyl-N-nitroso-p-toluenesulfonamide) with base, first discovered by de Boer and Backer,^{1,3} is also described on page 732 of the Aldrich Catalog 15⁴ (this catalog has the brewer on the cover).



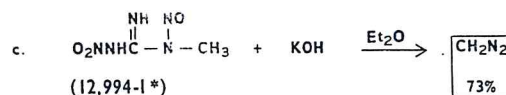
A second useful reagent is N,N'-dimethyl-N,N'-dinitrosoterephthalamide [bis-(N-methyl-N-nitroso)terephthalamide] described by Moore and Reed.²

This reagent was first developed by the E. I. du Pont de Nemours and Company under the trade name EXR-101.

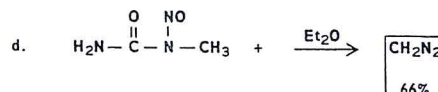


McKay⁵ has described the generation of diazomethane from N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). MNNG produces diazomethane with aqueous base and is thus easier to use than Diazald®, which requires alcoholic base.

A drawback is that many people become allergic to MNNG and it has been shown to be a potent mutagenic agent⁶ so it should be handled with great care.

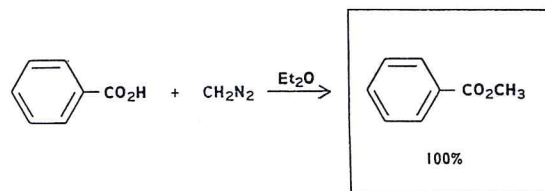


Finally, the use of methylnitrosourea is shown.⁷ This reagent was for many years the reagent of choice,⁸ but it must be stored in the refrigerator as it decomposes at room temperature.

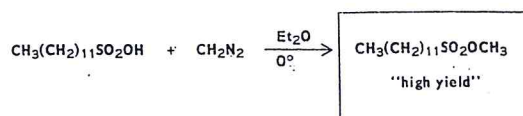


REACTIONS OF DIAZOMETHANE

(1) Methyl Esters from Carboxylic Acids⁷



(2) Methyl Sulfonates from Sulfonic Acids⁹

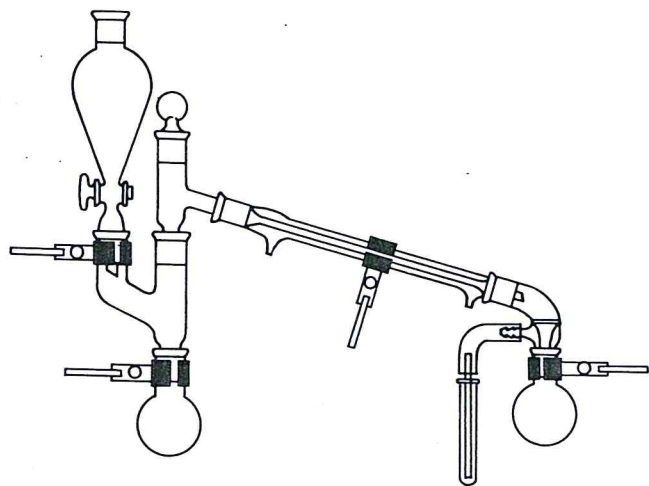


* Aldrich Catalog numbers

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DIAZOMETHANE PREPARATION



DIAZOMETHANE GENERATION

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The use of this kit exclusively for the preparation of diazomethane insures that necessary components will be kept together. A typical laboratory set-up is shown above. **ALL REACTIONS INVOLVING THE PREPARATION AND USE OF DIAZOMETHANE SHOULD BE CARRIED IN THE HOOD BEHIND A SAFETY SHIELD.** The glassware in the kit should be washed with care. Wire brushes should not be used as they can scratch the inner surface of the glassware.

Details of the laboratory preparation of diazomethane are included on the label of every bottle of Diazald[®]. They are repeated here for your convenience.

1. Preparation of ethereal alcoholic solutions of diazomethane.

Ethanol (95%, 25 ml) is added to a solution of potassium hydroxide (5 g) in water (8 ml) in a 100 ml distilling flask fitted with dropping funnel and an efficient condenser set downward for distillation. The condenser is connected in two receiving flasks in series, the second of which contains 20-30 ml ether. The inlet tube of the second receiver dips below the surface of the ether, and both receivers are cooled to 0°.

The flask containing the alkali solution is heated in a water bath to 65°, and a solution of 21.5g (0.1 mole) of Diazald[®] in about 200 ml of ether is added through the dropping funnel

in about 25 minutes. The rate of distillation should approximately equal the rate of addition. When the dropping funnel is empty, another 40 ml of ether is added slowly and the distillation is continued until the distilling ether is colorless. The combined ethereal distillate contains about 3 g of diazomethane.

2. Preparation of alcohol-free ethereal solutions of diazomethane.

2-(2-Ethoxyethoxy)-ethanol, our No. E455-0, (35 ml) and ether (20 ml) are added to a solution of potassium hydroxide (6 g) in water (10 ml). This solution is placed in a 125 ml flask fitted with a Claisen adapter dropping funnel, efficient condenser, and water bath at 70°. As the distillation of the ether starts, a solution of 21.5g of Diazald[®] in about 200 ml of ether is added through the dropping funnel over 20 minutes. During the distillation, the flask is occasionally shaken vigorously. The ethereal diazomethane is collected in the same manner as in 1. The yield is identical.

For the generation of about 6 g (0.15 mole) of diazomethane a 125 ml distilling flask and a 500 ml receiver are suggested. A review of the preparation and reactions of diazomethane published in *Aldrichimica acta*, 3,(4)9-12(1970) is available upon request.

Diazald[®] is probably the most useful reagent yet developed for the preparation of diazomethane. It is stable at room temperature for at least a year. (See, however, the precaution published in *Org. Syn. Coll. Vol. IV*, 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.") Diazald[®] is not a skin irritant to most people, though we recommend that all nitroso compounds be handled with care, and that contact with the skin be avoided.

Diazomethane is not only exceedingly toxic, but its solutions have been known to explode quite unaccountably. Hence, **ALL WORK WITH DIAZOMETHANE, regardless of how generated, SHOULD BE CARRIED OUT BEHIND SAFETY SHIELDS IN EFFICIENT HOODS.**

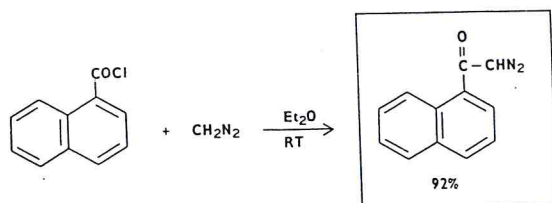
In most reactions of diazomethane, the presence of ethanol is not harmful; in some, a promoting influence is reported.¹ If the acid chloride is not too reactive, even the Arndt-Eistert reaction can be carried out in a medium containing alcohol.² In the reactions of diazomethane with reactive acid chlorides, with aldehydes, and in a few other reactions,³ ethanol must be absent. Procedure II is then used.

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(3) Enol Ethers from Carbonyl Compounds¹⁰

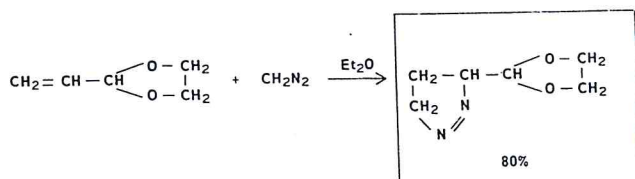
(11) Diazoketone Formation from Carboxylic Acid Halide²¹



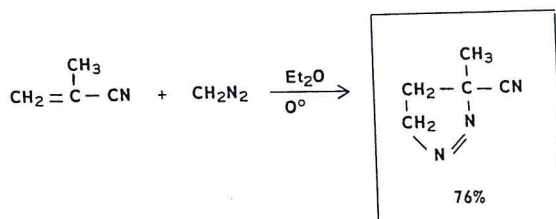
Diazoketones can be converted into acids²¹ (Arndt-Eistert Reaction) or α -chloroketones.²²

(12) Pyrazoline Formation

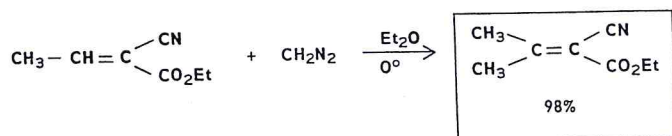
a. Simple Olefins²³



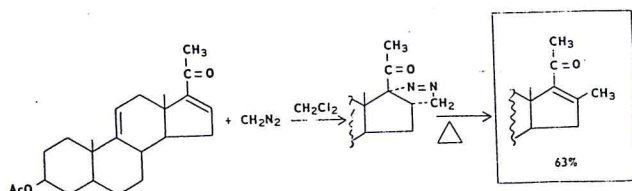
b. Activated Olefins²⁴



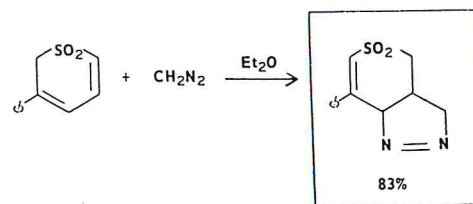
These pyrazolines produce cyclopropanes upon pyrolysis. The following olefin produced no pyrazoline.²⁵



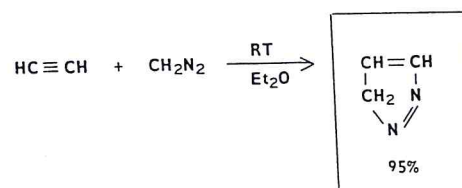
Another divergence is the pyrazoline decomposing to produce a methyl olefin rather than a cyclopropane.²⁶



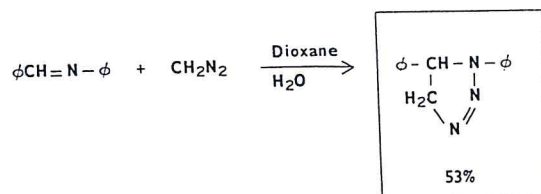
Finally, an example of pyrazoline formation accompanied by rearrangement has been reported.²⁷



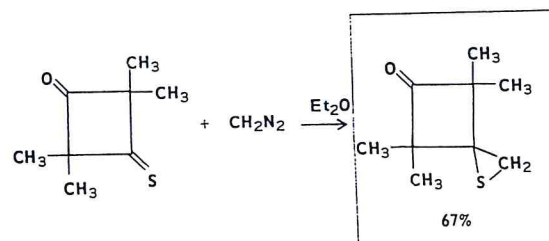
(13) Pyrazoles from Acetylenes²⁸



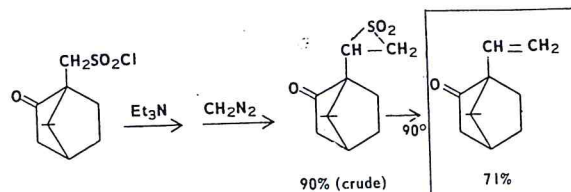
(14) Triazolines from Schiff's Bases²⁹



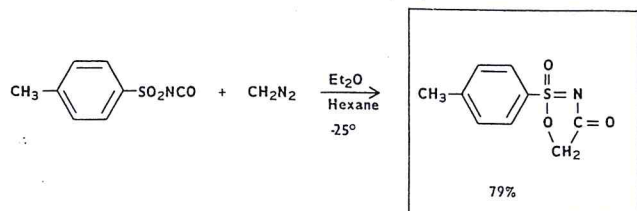
(15) Thiirane Ring Formation³⁰



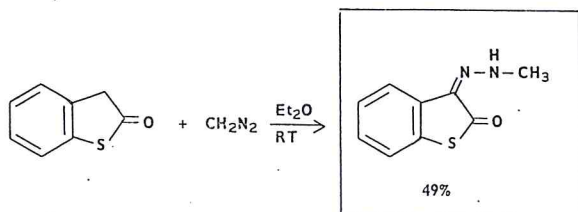
(16) Olefin Formation³¹



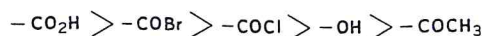
(17) Reaction with Sulfonylisocyanates³²



(18) Methylhydrazine Formation³³

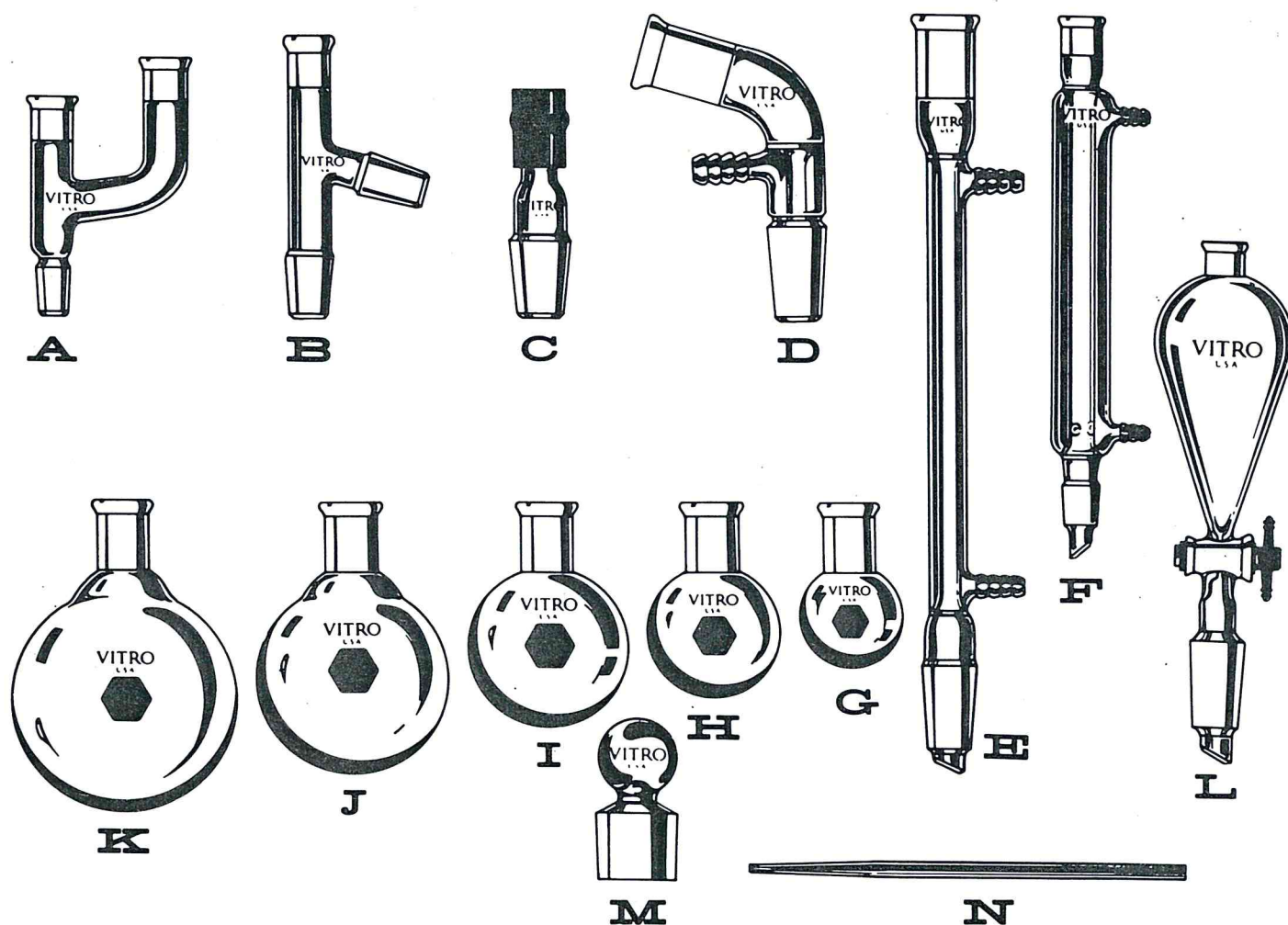


In conclusion the relative reactivity of functional groups toward diazomethane has been studied by Kosak³⁴ who found the order



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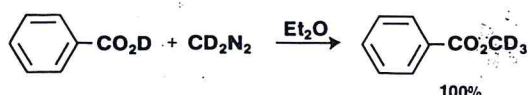
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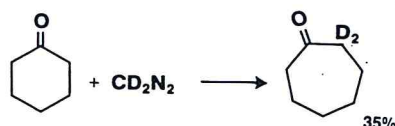
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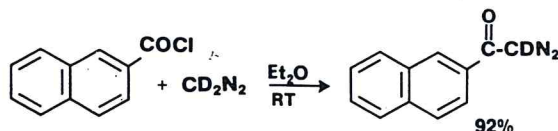
Methyl Esters from Carboxylic Acids²



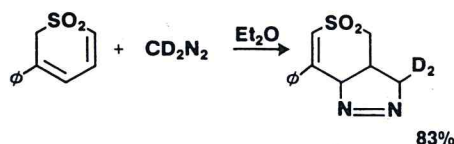
Ring Expansion of Ketones³



Diazoketone Formation from Carboxylic Acid Halides⁴



Pyrazolin Formation⁵



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