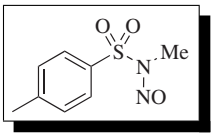
N-Methyl-*N*-nitroso-*p*-toluenesulfonamide



[80-11-5] $C_8H_{10}N_2O_3S$ (MW 214.27)

InChI = 1S/C8H10N2O3S/c1-7-3-5-8(6-4-7)14(12,13)10(2)9-11/h3-6H,1-2H3

InChIKey = FFKZOUIEAHOBHW-UHFFFAOYSA-N

(precursor of diazomethane[1a])

Alternate Names: Diazald; *p*-tolylsulfonylmethylnitrosamide.

Physical Data: mp 61–62 °C.

Solubility: sol petroleum ether, ether, benzene, alcohol, $CHCl_3$, CCl_4; insol H_2O.

Form Supplied in: pale yellow powder; commercially available.

Preparative Methods: prepared by the reaction of ***p-Toluenesulfonyl Chloride*** with methylamine, followed by nitrosation with ***Sodium Nitrite*** in glacial acetic acid.[1c]

Purification: recrystallization is best achieved by dissolving the reagent in hot ether (1 mL g^{-1}), adding an equal volume of petroleum ether (or pentane), and cooling in a refrigerator overnight.[1c]

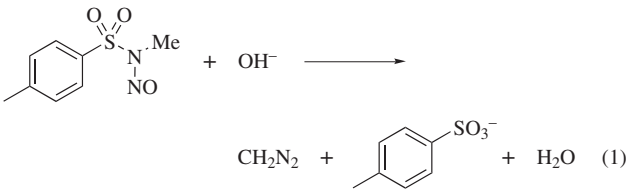
Handling, Storage, and Precautions: store in a brown bottle. Has a shelf-life of at least 1 year at rt. For longer periods of storage, it is recommended that the reagent be purified by recrystallization[1c] and refrigerated. Toxic; severe skin irritant; handle only in a fume hood.

Original Commentary

Yoshiyasu Terao & Minoru Sekiya
University of Shizuoka, Shizuoka, Japan

General Discussion. ***Diazomethane*** is a yellow gas (bp −23 °C, mp −145 °C) with the dipole structure $CH_2{=}N^+{=}N^-\ {}^+CH_2{-}N{=}N^-\ {}^-CH_2{-}N{=}N^+$. This versatile compound behaves as a methylene precursor with release of nitrogen and also functions as a 1,3-dipole in a variety of reactions, as documented in several reviews.[2] Diazomethane itself is both highly toxic and unpredictably explosive, and has been suggested to be a carcinogen.[3] Great care must be taken in handling this substance. However, these risks are minimal when diazomethane is prepared and handled as a dilute solution in an inert solvent such as ether using the proper equipment as discussed below (for further discussion, see ***Diazomethane***). A large number of compounds which previously served as diazomethane precursors can be represented by the formula RN(NO)Me, where R can be sulfonyl, carbonyl, imidoyl, or similar electron-withdrawing groups. Among these the reagent, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, introduced by de Boer and Backer in 1954,[1a] is the most common reagent used for the preparation of diazomethane. However, in some cases ***N-[N′-Methyl-N′-nitroso (aminomethyl)]benzamide*** and ***1-Methyl-3-nitro-1-nitrosoguanidine*** have advantages as diazomethane precursors. In addition, *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide does suffer from some drawbacks, including its relatively short shelf life (1–2 years) and its mutagenic activity.[4]

Diazomethane is prepared as a dilute solution in ether by the decomposition (eq 1) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide catalyzed by alkali hydroxide.



$$\text{+ } OH^- \longrightarrow CH_2N_2 + \text{+ } H_2O \quad (1)$$

This preparation and all reactions involving diazomethane should be carried out in an efficient fume hood and behind a sturdy safety shield. Rough surfaces and strong sunlight are known to initiate detonation. Carefully fire-polished glassware for diazomethane preparation is commercially available.[5] A typical experimental procedure is as follows.[1b] A 125 mL, 3-neck flask is charged with a solution of 6 g of potassium hydroxide in 10 mL of water, 35 mL of 2-(2-ethoxyethoxy)ethanol (carbitol), and 10 mL of ether, and is then fitted with an efficient condenser set downward for distillation. The condenser is connected to two receiving flasks in series, both cooled in an ice-salt bath. The second receiver contains 25 mL of ether and the inlet tube should dip below the surface of the solvent. The generating flask is heated in a water bath at about 70 °C, stirring is started (Teflon-coated magnetic stirring bar), and a solution of 21.4 g (0.1 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide in 125 mL of ether is added from the dropping funnel over about 20 min. The rate of addition should about equal the rate of distillation. When the dropping funnel is empty, 50–100 mL of additional ether is added slowly. The distillation is continued until the distilling ether is colorless. The combined ethereal distillate contains 2.7–2.9 g (64–69%) of diazomethane. The content of diazomethane in the codistilled ethereal solution can be determined by titration; excess benzoic acid is added to the solution (to react with diazomethane) and the excess acid is titrated with a standard solution of NaOH. If moisture must be removed from the ethereal diazomethane solution, the drying agent of choice is KOH pellets. It is recommended that diazomethane solutions be used immediately and not stored, even at low temperature.

An alternative popular procedure for the generation of small quantities (1–50 mmol) of diazomethane from Diazald employs a commercial 'mini-Diazald apparatus' with a dry-ice/acetone cold finger in place of the water-jacketed condenser.[5] The generation of diazomethane is carried out by treatment of the Diazald with KOH in aqueous ethanol.[2g]

First Update

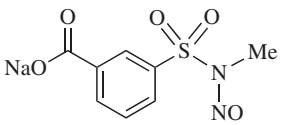
Rodrigo Ramírez-Contreras & Bill Morandi
Max-Planck-Institut für Kohlenforschung, Mülheim an der Ruhr, Germany

It is important to mention that during Carius tube tests, Diazald underwent a permanent gas generation event at ~60 °C, indicative of thermal instability.[6] Further testing showed Diazald to possess thermally initiated explosive properties, and a self-accelerating decomposition temperature lower than 75 °C.[6] Water can be used as a phlegmatizing agent for the purpose of transportation.[6]

In order to minimize the hazards posed by the generation and manipulation of ethereal solutions of diazomethane, even in small quantities, safer protocols have relied on an in situ approach to the generation and use of diazomethane. Flow chemistry techniques can be particularly advantageous. In these systems, diazomethane is generated on demand in small quantities from Diazald and KOH, separated from the aqueous phase by diffusion through a suitable semipermeable membrane and used immediately. Designs of such systems include tube-in-tube reactors[7] and dual-channel microreactors.[8]

Following a similar rationale, but for the industrial generation of diazomethane (>50 tons per year), the design of a continuous process has been reported where formation of the gas is controlled by simultaneous feeding of a solution of Diazald in a solvent of low vapor pressure, such as DMSO, and an aqueous solution of KOH into a reactor with continuous sparging with an inert gas, in order to achieve a high head-space concentration of diazomethane. The gas formed can then be used in the next downstream reaction.[6]

In a recent development, a biphasic method has been designed wherein diazomethane generated from the water soluble nitrosamine (2) in aqueous 6 M KOH is immediately consumed in an in situ, tandem iron-catalyzed carbene transfer process taking place in the organic phase.[9] Generation of diazomethane is controlled by the rate of addition of (2) to the reaction mixture, therefore avoiding the buildup of hazardous amounts of diazomethane. This method has been used in the cyclopropanation of styrenes to yield the desired products in excellent yields.[9]



(2)

Generation of ^{13}C- and D-Labeled Diazomethane. Preparation of *N*-$^{13}CH_3$ and *N*-CD_3 labeled Diazald in yields upwards of 90% has been recently described[10] by methylation of N-Boc-*p*-toluenesulfonamide using ^{13}C-methyl- or methyl-d_3-*p*-toluenesulfonates, respectively, formed from $^{13}CH_3OH$ or CD_3OH and *p*-toluenesulfonyl chloride, triethylamine, and catalytic amounts of $Me_3N{\cdot}HCl$.[11]

Nitrosyl Transfer Reactions. The nitroso group of Diazald can be transferred by nucleophilic attack on the N=O group, a process known as transnitrosation. Nitroso group transfer to amines, amides, and thiols is of biochemical significance in vivo.[12] Denitrosation of Diazald takes place in Brønsted acidic media.[12a]

Diazald has been used as a milder nitrosyl-group transfer agent alternative to $[NO][XF_n]$ salts (X = B, n = 4; X = P, n = 6) in the synthesis of NO complexes of Va,[13] Nb,[14] Ta,[14] Mo,[15] W,[15b,c] Cr,[15d] Fe,[16] Ru,[17] Rh,[18] Ir,[19] and Pd.[20]

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