SYNLETT
Spotlight 212

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Diazomethane (CH_2N_2)

Compiled by Eva Šťastná

Eva Šťastná was born in 1980 in Ostrava (Czech Republic). She received her M.Sc. in organic chemistry from Charles University, Prague in 2004. Currently she is working towards her Ph.D. under the supervision of Dr. Hana Chodounská in the Institute of Organic Chemistry and Biochemistry of the Academy of Sciences of the Czech Republic in Prague. Her research interests are focused on the synthesis of neurosteroids as potential inhibitors of the NMDA-receptor.

Department of Steroid Chemistry, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 166 10 Prague, Czech Republic
E-mail: stastna@uochb.cas.cz

Introduction

Diazomethane (CH_2N_2, **1**) is one of the most versatile and indispensable reagents in organic chemistry.[1] It is principally employed for the methylation of compounds containing active hydrogen, in cycloadditions, and one-carbon chain elongation/ring expansion. The main advantage of diazomethane over other methylating agents lies in its usage in neutral media, very often at low or room temperature, and in the absence of non-volatile byproducts.

Diazomethane is usually used as a solution in diethyl ether. It can be generated by reaction of alkali hydroxide with various derivatives of *N*-methyl-*N*-nitrosoamines, such as *N*-methyl-*N*-nitroso-4-toluenesulfonamide (Diazald®, **2**), 1-methyl-3-nitro-1-nitrosoguanidine (MNNG, **3**), or *N*-methyl-*N*-nitrosourea (**4**).

The structure of CH_2N_2 may be expressed by the following mesomeric forms to explain its basic (**1a** and **1b**), electrophilic (**1c**), or nucleophilic character (**1b**).

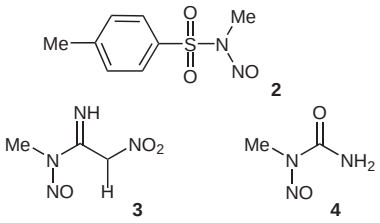
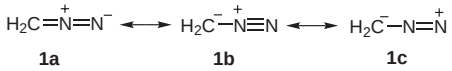


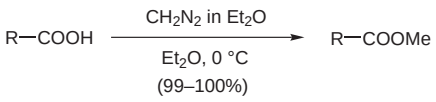
Figure 1



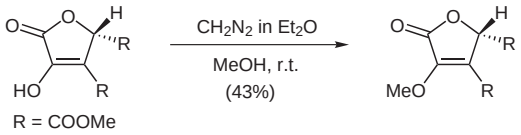
Scheme 1

Abstracts

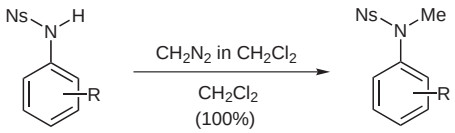
(A) *Preparation of Methyl Esters:*
Methylation of carboxylic acids with CH_2N_2 is an efficient and well-known method. Lee H. J. et al. described esterification of abietic, levopimaric, palusteric, and neoabietic acids in almost quantitative yields.[2]



(B) *Preparation of Methyl Ethers:*
The reaction of CH_2N_2 with alcohols usually proceeds in the presence of a catalyst. The most favoured catalysts are boron trifluoride-etherate and fluoboric acid. Chithra et al. described a simple methylation of the hydroxy group of an enolic lactone in the absence of a catalyst.[3]

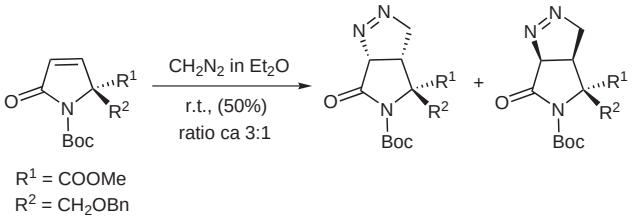


(C) *Preparation of N-Methyl Compounds:*
The methylation of compounds containing an –NH group usually occurs readily and often gives high yields of the desired product. Usage of an appropriate N-protecting group enhanced the acidity of the amine proton that leads to rapid N-methylation of various derivatives of aniline with very high yield.[4]

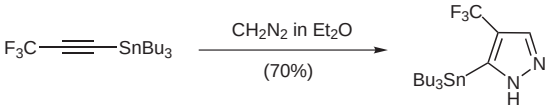


SYNLETT 2007, No. 15, pp 2454–2455
Advanced online publication: 22.08.2007
DOI: 10.1055/s-2007-985599; Art ID: V21507ST

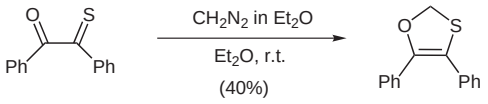
(D) *Cycloadditions Leading to Pyrazolines:*
The addition of CH_2N_2 to a wide variety of compounds containing a C–C double bond has been found to give pyrazolines in high yields. The initial pyrrolidinone was converted into the mixture of two pyrazolines via 1,3-dipolar cycloaddition.[5]



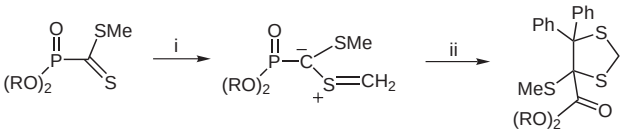
(E) *Cycloadditions Leading to Pyrazoles:*
Pyrazoles can be prepared by reaction between CH_2N_2 and derivatives of tributyl(3,3,3-trifluoro-1-propynyl)stannane.[6]



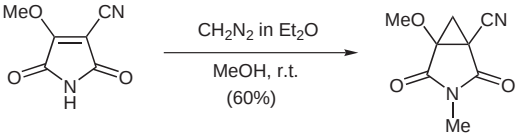
(F) *Cycloadditions Leading to 1,3-Oxathiols:*
1,3-Oxathiols can be prepared by reaction of α-thioxo ketones with diazomethane.[7]



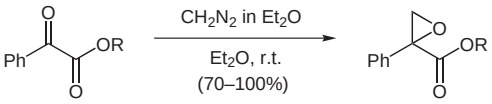
(G) *Cycloadditions Leading to 1,3-Dithiolans:*
The work of Mlostoń et al. describes reactions of CH_2N_2 with α-oxo dithioesters which lead to the formation of the corresponding sulfoniomethanide.[8] The subsequent reaction with diphenylmethanthione gave the expected dithiolanes.



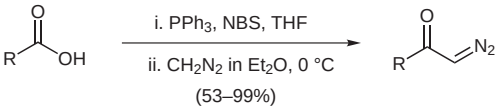
(H) *Cycloadditions Leading to a Cyclopropane Ring:*
The formation of cyclopropane by the reaction of CH_2N_2 with an alkene can occur via formation of an unstable pyrazoline which may then lose nitrogen directly, or by the application of heat, to form the cyclopropane. The work of Poschenrieder et al. described the direct formation of cyclopropane derivatives in high yields by treatment of substituted maleimides with CH_2N_2 at room temperature.[9]



(I) *Cycloadditions Leading to Epoxides:*
Diazomethane will add to aldehydes or ketones to give epoxides and/or homologous compounds. Petronijevic et al. reported uncatalyzed reactions of diazomethane with benzoylformate esters derived from terpenic alcohols that resulted in the formation of α-oxiranyl esters in high yields.[10]



(J) *Preparation of α-Diazoketones:*
Cuevas-Yañez et al. described the reactions of various homocyclic and heterocyclic aromatic carboxylic acids, simple aliphatic carboxylic acids and α-substituted acetic acid derivatives with diazomethane, which afforded the desired α-diazoketones.[11]



References

(1) *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons Ldt.: New York, **2006**.
(2) Lee, H. J.; Ravn, M. R.; Coates, R. M. *Tetrahedron* **2001**, *57*, 6155.
(3) Chitra, G.; Salini, T.; Nair, M. S.; Ibnusaud, I. *Tetrahedron Lett.* **2006**, *47*, 7957.
(4) Pera, A.; Leggio, A.; Liguori, A. *Tetrahedron* **2006**, *62*, 6100.
(5) Caubert, V.; Langlois, N. *Tetrahedron Lett.* **2006**, *47*, 4473.
(6) Hanamoto, T.; Hakoshima, Y.; Egashira, M. *Tetrahedron Lett.* **2004**, *45*, 7573.
(7) Egli, D. H.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2006**, *89*, 1910.
(8) Mlosto, G.; Urbaniak, K.; Gulea, M.; Masson, S.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **2005**, *88*, 2582.
(9) Poschenrieder, H.; Stachel, H. D.; Eckl, E.; Jax, S.; Polborn, K.; Mayer, P. *Helv. Chim. Acta* **2006**, *89*, 971.
(10) Petronijevic, F.; Hart, A. C.; Paquette, L. A. *Tetrahedron Lett.* **2006**, *47*, 1741.
(11) Cuevas-Yañez, E.; Garcia, M. A.; Mora, M. A.; Muchowski, J. M.; Cruz-Almanza, R. *Tetrahedron Lett.* **2003**, *44*, 4815.