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The Reagent

Trimethylsilyldiazomethane ($TMS\text{-}CHN_2$) and Lithiated Trimethylsilyldiazomethane – Versatile Substitutes for Diazomethane

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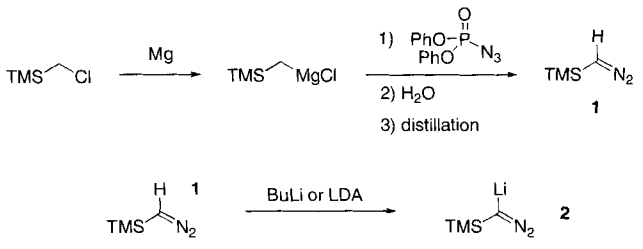
Diazomethane, though intensively used in organic synthesis [1, 2], is notoriously dangerous to handle, since it is highly toxic, thermally labile and potentially explosive [3]. Due to these hazards, its substitute trimethylsilyldiazomethane (**1**) is becoming increasingly used in numerous applications [4–6]. It is much less toxic, thermally stable and non-explosive [7].

Several synthetic approaches for the title compound **1** have been published [5, 8] since its first preparation by Lappert *et al.* [9]; an Organic Syntheses procedure allows for a large scale preparation, starting with chloromethyl-trimethylsilane (Scheme 1) [10]. In addition it can be purchased as a 2M hexane solution from Aldrich; its molarity is constant over a long period – or, if it is in doubt, it can be accurately determined by published methods [10]. The deprotonation of **1** with butyllithium or lithium diisopropylamide (LDA) yields its lithiated derivative **2** (Scheme 1) [11], which is a useful supplement to the applicability of the parent compound **1**.

Usually, TMS-diazomethane (**1**) reacts as a nucleophile, especially its lithiated derivative **2** (Arndt-Eistert homologation, homologation of ketones and aldehydes). Nevertheless, after protonation, reactivity can be inverted and the reagent acts as an electrophil (*O*-methylation). In cyclizations it can act as a [C–N–N] synthon (1,3-dipolar cycloadditions) or as a C-1 unit (carbenoid chemistry – cyclopropanations and alkenylidene-reactions).

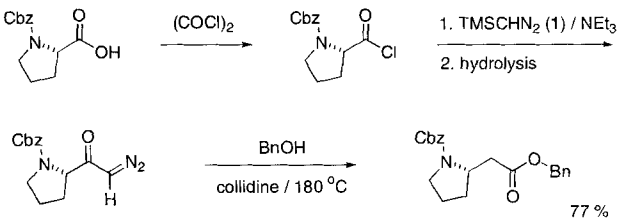
Herein, we will focus on the major applications of compounds **1** and **2** in organic synthesis, which are dominated by the pioneering work of Aoyama and coworkers (*vide infra*). The utilization of silylated diazomethanes **1** and **2** in the preparation or modification of transition metal complexes and main group compounds would be beyond the scope of this short-review.



Scheme 1 Preparation of trimethylsilyldiazomethane **1** [10] and its lithiated derivative **2** [11]

Arndt-Eistert Homologation

TMS-CHN2 (**1**) can be used for the Arndt-Eistert homologation of carboxylic acids: Though it seems to be less reactive than diazomethane (most probably for steric reasons), since it does not react with amino acid derivatives activated as mixed anhydrides, it can be used for a chain elongation starting with acid chlorides. In a first step, diazoketones are formed (the C–Si-bond is cleaved hydrolytically during work-up) [7], which can be rearranged thermally, photochemically or metal catalyzed [12] to the corresponding acid derivatives (Scheme 2) [7, 13].

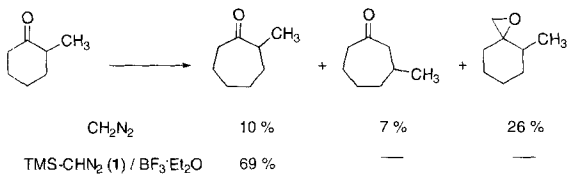


Scheme 2 Arndt-Eistert homologation of Cbz-proline using $TMS\text{-}CHN_2$ [7]

Homologation of Ketones and Aldehydes

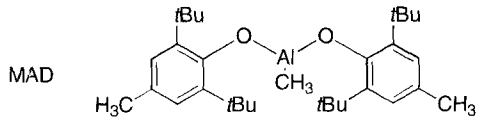
Ketones, especially cyclic ketones can be homologated with $TMS\text{-}CHN_2$ [14–17], which, due to steric reasons, often give rise to more definite products than diazomethane (Scheme 3) [18].

The presence of Lewis acids seems to be essential in this reaction; etheral BF_3 [14, 15] or organoaluminium compounds [16, 17] are used generally. The favourable consequences of the steric bulk in $TMS\text{-}CHN_2$ can be additionally improved by the sterically demanding Lewis acid MAD [methyl



Scheme 3 Homologation of 2-methylcyclohexanone with TMS-CHN_2 [15] or diazomethane [18]

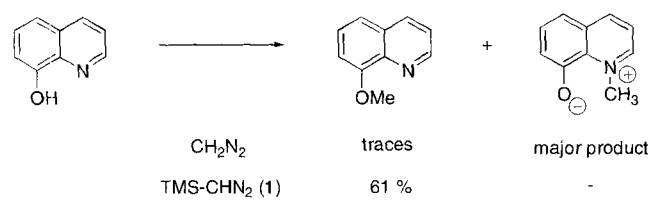
aluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide)] which leads to even better product ratios [16]. In the homologation of aldehydes with TMS-CHN_2 an anionotropic migration of the aldehyde-hydrogen leading to methyl ketones is observed predominantly [16, 19–21]. The Si-C bond is usually cleaved during the reaction [20]. Though the presence of Lewis acids is not essential, it still seems to be favourable and again, MAD gives best results [16, 21].



O-Methylation

The preparation of methyl esters from carboxylic acids can be achieved with silylated diazomethane **1** when methanol is used as a solvent [22]. ^{13}C isotope labeling experiments [5] showed that TMS-CHN_2 rather than methanol is incorporated to form the methyl moiety. Actually, methanol is necessary for the methanolysis of the C–Si bond during this reaction. The *O*-methylation of amino acids is possible [22], nevertheless, a better performance can be achieved, when *N*-protected amino acids are used [23]. Maleic anhydrides react with TMS-diazomethane to yield the corresponding diesters [24].

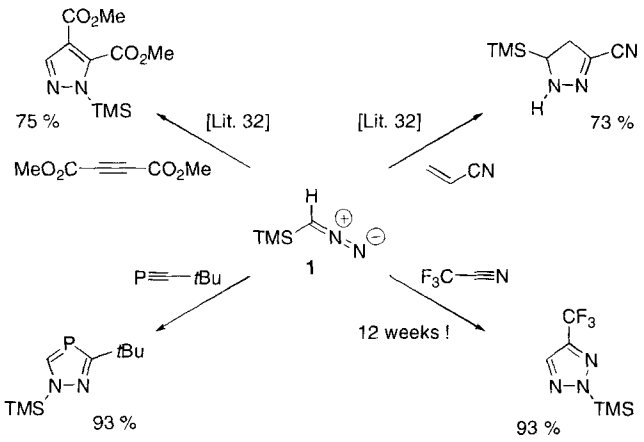
As with diazomethane, primary, secondary and tertiary alcohols can be transformed to methyl ethers with TMS-CHN_2 in the presence of HBF_4 [25]. Phenols and enols, respectively, react in the presence of Hünig's base ethyl diisopropyl amine [26]. Yields are mostly comparable with those obtained with diazomethane, but in some cases the results are significantly better: *e.g.* methylation of 8-hydroxyquinoline with the title compound **1** yields the corresponding methyl ether in 61% yield [26], whereas with diazomethane the methyl ether is formed in trace amount; the major product is the *N*-methylated betaine (Scheme 4) [27].



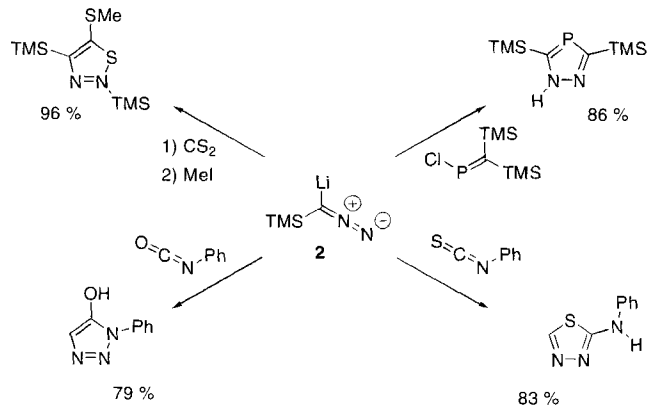
Scheme 4 Methylation of 8-hydroxyquinoline with diazomethane [27] or TMS-CHN_2 [26], respectively

Formation of Diazole Heterocycles

TMS-diazomethane can be used for cycloadditions with compounds bearing multiple bonds leading to diazole derivatives. In most cases these [3+2] cycloadditions cannot be described as concerted reactions but take place as multistep reactions, starting with a nucleophilic attack of the TMS-CHN_2 at the multiple bond. Consequently, in some cases the usage of the more nucleophilic lithiated derivative **2** is favourable or even essential to obtain good results. Most of these reactions can also be performed with diazomethane with some exceptions: Reaction of *e.g.* CS_2 proceeds not with diazomethane, but works well with lithiated TMS-CHN_2 (Scheme 6) [28]. Besides this, another advantage is connected with the usage of the silylated 1,3-dipole **1**. The cycloadditions generally lead to silylated products; the silyl group can either be cleaved hydrogenolytically or fluoride-induced or, what is more favourable for organic synthesis, used for group transformations and even C–C couplings. Some examples for cycloadditions using diazomethane derivatives **1** and **2** are depicted



Scheme 5 Cycloadditions to pyrazoles [32, 33], dihydropyrazoles [8, 32–37], triazoles [38], and 1,2,4-diazaphospholes [39]

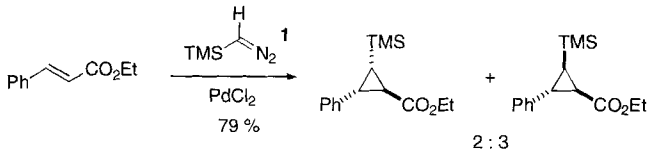


Scheme 6 Cycloadditions with **2** leading to 1,2,3-thiadiazoles [28], 1,2,4-diazaphospholes [40], 2-amino-1,3,4-thiadiazoles [41], and 1,2,3-triazoles [42]

in schemes 5 and 6. In some cases a migration of the silyl-group leads to *N*-silylated products. Tetrazoles [29, 30], oxadiazoles [30], 1,2,3-thiadiazoles [28, 30] and 1,2,3,4-diazadiphospholes [31] can be obtained in analogous cycloadditions.

Formation of Cyclopropanes

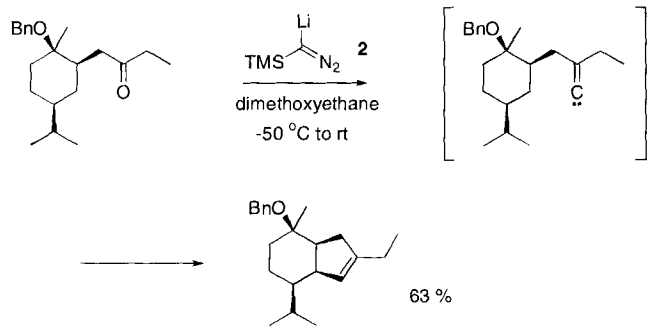
Cyclopropanation of olefins with TMS-diazomethane under catalytic ($PdCl_2$ or CuCl) or photochemical conditions leads to synthetically useful silylcyclopropanes [43, 44]. Nevertheless, the yields are generally low, usually not exceeding 50%. While electron-rich alkenes cannot be transformed at all, acceptor-substituted olefins give reasonably good results (Scheme 7) [44]. Tetracyanoethylene for example gives rise to the corresponding cyclopropane in an exceptional 97% yield.



Scheme 7 Cyclopropanation of ethyl cinnamate with TMS-diazomethane [44]

Alkylidene–Carbene Reactions

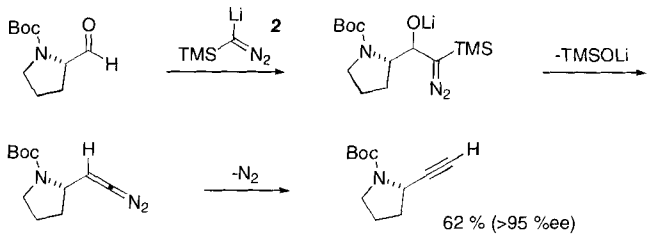
Nucleophilic attack of the lithiated diazomethane derivative **2** at carbonyl compounds leads to intermediates, which after loss of silanolate and dinitrogen give carbenes (alkylidene carbenes). These carbenes (or carbenoids) are stabilized either by intramolecular insertions in C–H [45–54], N–H [55, 56] or O–H bonds [57] (Scheme 8) or by rearrangement in a Fritsch-Buttenberg-Wiechell-like reaction Colvin rearrangement to form alkynes (Scheme 9) [58 – 60].



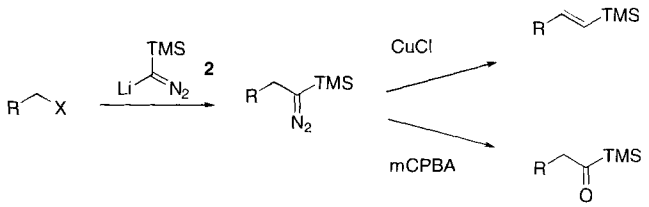
Schema 8 Insertion of a carbene in a C-H bond [53]

Preparation of TMS-substituted Diazoalkanes

S_N2-reaction of **2** with haloalkanes [61] or transformation of **1** with alkanesulfonyl chlorides [62] gives rise to the corresponding TMS-diazoalkanes, which can be reacted further to afford (*E*)-alkenes by means of CuCl [61] or yield ketones by oxidation with *m*-chloroperbenzoic acid (mCPBA) (Scheme 10) [63].



Scheme 9 Colvin rearrangement of prolinal [60]



Schema 10 Preparation of TMS-diazoalkanes and further transformation to (*E*)-alkenes [61] or ketones [63]

Conclusion

TMS-diazomethane (**1**) and its lithiated derivative **2** are stable and safe substitutes for hazardous diazomethane. They show similar reactivity as diazomethane (both as C-1 introducing agent and as [C–N–N] synthon) and sometimes lead to even better yields and selectivities. A plethora of different reactions of silylated diazomethanes **1** and **2** has been examined; we are looking forward to further development and applications in this area.

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