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Trimethylsilyldiazomethane – A Mild and Efficient Reagent for the Methylation of Carboxylic Acids and Alcohols in Natural Products

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Summary. Esterification of various naturally occurring carboxylic acids with trimethylsilyldiazomethane proceeds nearly quantitatively under very mild conditions. Furthermore, highly sterically hindered alcohols can be converted directly to the corresponding methyl ethers. Improved methods for the preparation and quantification of this reagent are described.

Keywords. Trimethylsilyldiazomethane; Methylation; Carboxylic acids; Alcohols; Natural products.

Introduction

Diazomethane (CH_2N_2) is a well-known reagent for methylations [1], but it is highly toxic, thermally labile, and explosive. These disadvantages can be overcome by replacement of one hydrogen of CH_2N_2 by a trimethylsilyl group. The resulting safe and stable trimethylsilyldiazomethane (*TMS*CHN_2, **1**) was initially employed mainly for analytical purposes [2]. In the course of the development of methods for the large-scale preparation of *TMS*CHN_2, this substitute is increasingly used in synthetic applications [3].

In this paper we focus on the improvement of O-methylation of naturally occurring carboxylic acids and alcohols and demonstrate that *TMS*CHN_2 is more than a non-toxic alternative to diazomethane. In addition, we developed a simplified method for the preparation and a novel and facile quantification procedure to enable a broad applicability in partial-synthetic work.

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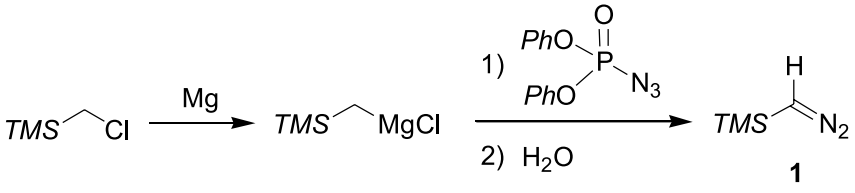
Results and Discussion

Preparation of Trimethylsilyldiazomethane

Since *Lappert* and *Lorberth* [4] reported the first preparation of *TMS*CHN_2 in 1967, several synthetic approaches for the preparation of the title compound **1** have been published. Among these methods, the diazo-transfer reaction of trimethylsilylmethylmagnesium chloride with diphenyl phosphorylazidate (*DPPA*) [5] (Scheme 1) is the method of choice, because it is most practical and allows a high-yield and large-scale preparation. *DPPA* is commercially available. However, we prepared this precursor in a modified way of the synthesis described in Ref. [6]. The large-scale synthesis of *TMS*CHN_2 is characterised by a very extensive purification followed by a change of the solvent system from Et_2O to *n*-hexane [5]. We found that the transfer to *n*-hexane is not necessary, because the original Et_2O solution is also reactive and can be stored without decomposition for several months.

Determination of the Concentration

The quantification procedure of **1** by NMR (Ref. [5]) is rather complex and impractical. We developed a simple UV-spectroscopic method to determine the concentration of the final etheric solution. The UV-spectrum of **1** shows two maxima at 237.0 and 402.0 nm. To minimize interference with aromatic impurities we chose the less intensive UV-maximum at 402.0 nm ($\varepsilon = 25.9\,\mathrm{dm^3\,mol^{-1}\,cm^{-1}}$) for this



Scheme 1

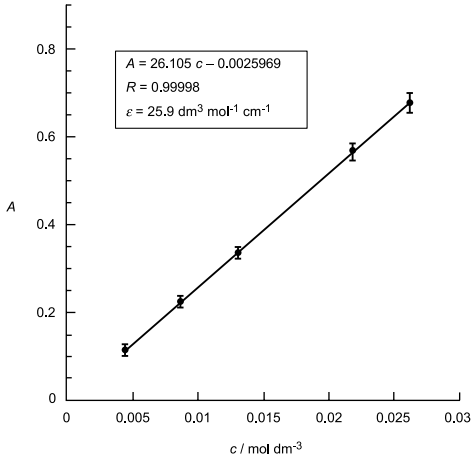


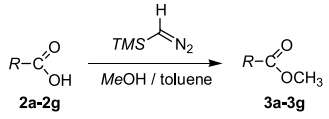
Fig. 1. Calibration graph of *TMS*CHN_2 in etheric solution

purpose. The calibration was done with five authentic samples purchased from Sigma-Aldrich. Each one was measured at five dilutions in triplicate or duplicate. The resulting graph shows a high linearity (R) in the range between 5–25 mmol dm^{-3} with small deviation (Fig. 1), thus the concentration of **1** can be determined via ε or the linear equation.

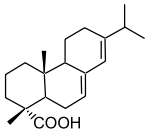
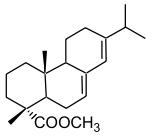
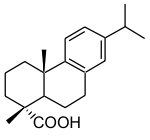
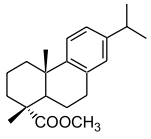
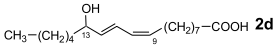
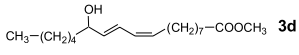
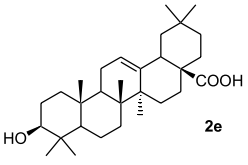
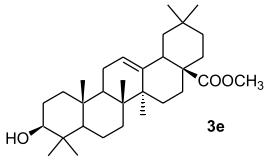
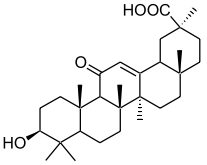
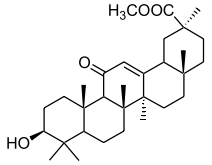
Preparation of Methyl Esters

Naturally occurring carboxylic acids are cheap, easily available, and enantiomerically pure starting materials for the partial synthesis of biologically active compounds. In many synthesis strategies the conversion to the methyl ester is thereby required [7–11]. The preparation of methyl esters from carboxylic acids can be

Table 1. Methylation of some natural occurring carboxylic acids



2a-2g **3a-3g**

Entry	Carboxylic acid	Product	Yield/%
1	$CH_3-(CH_2)_7$ $(CH_2)_7-COOH$ **2a**	$CH_3-(CH_2)_7$ $(CH_2)_7-COOCH_3$ **3a**	96
2	 **2b**	 **3b**	94
3	 **2c**	 **3c**	99
4	 **2d**	 **3d**	96
5	 **2e**	 **3e**	94
6	 **2f**	 **3f**	91
7	 **2g**	 **3g**	99*

* GC-yield; after CC 83% isolated product

achieved with *TMS*CHN_2 in methanolic benzene. In the reported procedure a home-made solution of *TMS*CHN_2 in benzene was used for GC-analysis of fatty acids [2].

We tested the reactivity of the etheric solution of this reagent with various natural compounds (di- and triterpenic acids, fatty acids) and found it to be active even in synthetic scales. Because of its toxicity, benzene was replaced by toluene in our method.

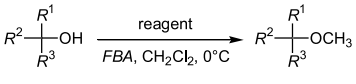
All esterifications proceeded instantaneously and nearly quantitatively without any influence of other functional groups. The reaction was easily monitored by the disappearance of the yellow colour of *TMS*CHN_2. The results are summarized in Table 1.

Preparation of Methyl Ethers

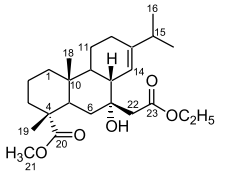
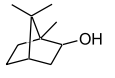
Alcoholic hydroxyl groups can be methylated by diazomethane under very mild conditions [12]. For this reason this reagent was frequently used for the methylation of alcohols containing other sensitive groups. *Aoyama* and *Shioiri* reported the methylation of unhindered and moderately hindered primary, secondary, and tertiary alcohols with *TMS*CHN_2 in the same way [13]. Yields were comparable with those obtained by diazomethane, but in certain cases the results were significantly better [14].

We report here the methylation of the highly sterically hindered alcohols **4a** and **4b**, which were found to be extremely inert to diazomethane and other electrophilic reagents [12, 15, 16]. We compared the etherification with diazomethane (method described by *Neeman*) and with *TMS*CHN_2 (*Aoyama*'s method). The reaction of **4a** and **4b** with *TMS*CHN_2 yielded the respective methyl ethers in medium yields, whereas the methylation with diazomethane failed. The successful methylation was carried out in CH_2Cl_2 at 0°C in the presence of *FBA*. The results are summarized in Table 2.

Table 2. Methylation of some highly sterically hindered alcohols



4a,4b **5a,5b**

Entry	Alcohol	Reagent	Yield/%
1	 **4a**	*TMS*CHN_2	42
		CH_2N_2	0
2	 **4b**	*TMS*CHN_2	51
		CH_2N_2	0

Experimental

Melting points were obtained on a digital melting point apparatus Büchi 535. Optical rotation: polarimeter 241 MC (Perkin Elmer). IR spectra: infrared spectrometer system 2000 FT (Perkin Elmer). UV-VIS: UV-160A UV-visible recording spectrophotometer (Shimadzu). NMR spectra: Varian Unity Inova 400 (300 K) 5 mm tubes, *TMS* resonance as internal standard. ^{1}H- and ^{13}C-resonances were assigned using ^{1}H,^{1}H- and ^{1}H,^{13}C-correlation spectra. HMBC spectra were optimized for 8 Hz. ^{1}H- and ^{13}C-resonances are numbered as given in the formulae. Assignments marked with an asterisk are interchangeable. Mass spectra: GC/MS-Detektor HP 6890, 70 eV electron impact; ESI-MS: Finnigan LCQ Deca XP Plus ion trap mass spectrometer configurated for positive ionisation; HR-MS: PE-SCIEX QStar QTOF mass spectrometer using the Ionspray source in the positive ESI mode, exact mass calibration with quinine giving $m/z = 325.1916$ (100%), $[MH]^+$. Materials: Column-chromatography (CC): silica gel 60 (Merck, 70–230 mesh), pore-diameter 60 Å; solvents: cyclohexane:ethyl acetate (=*CH*:*Et*O*Ac*), dichloromethane:ethyl acetate; thin-layer chromatography (*TLC*): *TLC* plates (Merck, silica gel 60 F_{254}, 0.2 mm, 200×200 mm); the compounds were detected in UV light at 254 nm as well as by spraying with molybdatophosphoric acid and by subsequent heating with a heat gun.

Preparation of Trimethylsilyldiazomethane (**1**, $C_4H_{10}N_2Si$)

A: Diphenylphosphoryl Azide (DPPA)

To a suspension of 7.22 g (111 mmol) of NaN_3 in 80 cm^3 of anhydrous acetone 14.9 g (55.6 mmol) of diphenylphosphoryl chloride were added and stirred at room temp. for 21 h. The suspension was filtered and the solvent removed under reduced pressure. The residual oil was extracted with anhydrous Et_2O to give the phosphoryl azide as a nearly colourless oil (12.4 g, 81%).

B: Trimethylsilylmethylmagnesium Chloride

Mg turnings (1.46 g, 60.0 mmol) were suspended in 20 cm^3 of anhydrous Et_2O and treated with 20 mm^3 of 1,2-dibromoethane to activate the Mg. After stirring at room temp. for 15 min, 1/10 of a solution of 6.13 g (50.0 mmol) of chloromethyltrimethylsilane in 20 cm^3 of anhydrous Et_2O were added at once. When the reaction had started, the remaining solution was added dropwise at such a rate that a gentle reflux was maintained throughout the addition. After complete addition, stirring was continued for 1 h at 40°C to give the *Grignard* reagent.

C: Trimethylsilyldiazomethane

A solution of 12.4 g (45.0 mmol) of *DPPA* in 50 cm^3 of anhydrous Et_2O was cooled to −10°C with a NaCl/ice cooling bath. The *Grignard* reagent prepared above was added dropwise at such a rate that the internal temperature maintained below 0°C. The mixture was stirred at 0°C for 2 h, then allowed to stand in an ice bath overnight. After cooling to −10°C, the mixture was slowly treated with about 5 cm^3 of cold H_2O. The resulting white precipitate was filtered with suction and washed with cold Et_2O several times. It is recommended to cool the suction flask during filtration. The combined organic layers were washed with ice-water and dried over Na_2SO_4 yielding 127 cm^3 of a 0.28 *M* solution of *TMS*CHN_2 (79%). This solution was enriched by distillation over a packed column to a final concentration of approximately 1 *M*. The reagent was used without further purification. It can be stored at 4°C without decomposition for at least 6 months. ^{1}H NMR (400 MHz, Et_2O-d_{10}): $\delta = 0.09$ (s, $(CH_3)_3Si$), 2.62 (s, HC=N) ppm; ^{13}C NMR (100 MHz, Et_2O-d_{10}): $\delta = -1.0$ ($(CH_3)_3Si$), 19.6 (HC=N) ppm; UV-Vis (Et_2O): λ_{max} (lgε) = 237.0 (3.98), 402.0 (1.41) nm; EI-MS (70 eV): m/z (%) = 114 (52) $[M]^+$, 99 (52), 58 (100).

General Procedure for the Preparation of Methyl Esters

To a stirred solution of the carboxylic acid (1 mmol) in approximately 10 cm^3 of toluene:*Me*OH (3:2) an etheric solution of *TMS*CHN_2 was added dropwise until the yellow colour persisted (1.1–1.5 mmol). The mixture was stirred for 30 min at room temperature and concentrated to give the corresponding methyl ester.

Methyl oleate (**3a**)

The product was purified by CC using *CH*:*Et*OAc = 5:1 as eluent. Yield 96%; pale yellow oil; $R_f = 0.53$ (silica, *CH*:*Et*OAc = 5:1); NMR-data are in accordance with those reported in Ref. [17].

Methyl abietate (**3b**)

The product was purified by CC using *CH*:*Et*OAc = 9:1 as eluent. Yield 94%; pale yellow oil; $R_f = 0.40$ (silica, *CH*:*Et*OAc = 9:1); NMR-data are in accordance with those reported in Refs. [18, 19].

Methyl dehydroabietate (**3c**)

The product was purified by CC using *CH*:*Et*OAc = 9:1 as eluent. Yield 99%; white crystals, mp 61–62°C; $R_f = 0.48$ (silica, *CH*:*Et*OAc = 9:1); NMR-data are in accordance with those reported in Ref. [20].

Methyl 13-hydroxylinoleate (**3d**)

The product was purified by CC using *CH*:*Et*OAc = 2:1 as eluent. Yield 96%; pale yellow oil; $R_f = 0.40$ (silica, *CH*:*Et*OAc = 2:1); NMR-data are in accordance with those reported in Ref. [21].

Methyl oleanolate (**3e**)

The product was purified by recrystallization from anhydrous *Me*OH. Yield 94%; white solid, mp 200–202°C; $R_f = 0.59$ (silica, CH_2Cl_2:*Et*OAc = 3:1); NMR-data are in accordance with those reported in Refs. [22, 23].

Methyl glycyrrhetate (**3f**)

The product was purified by recrystallization from *Et*OH:H_2O (1:1). Yield 91%; white crystals, mp 248–250°C; $R_f = 0.41$ (silica, CH_2Cl_2:*Et*OAc = 4:1); NMR-data are in accordance with those reported in Ref. [24].

Methyl salicylate (**3g**)

The product was purified by CC using *CH*:*Et*OAc = 2:1 as eluent. Yield 83%; colourless oil; $R_f = 0.50$ (silica, *CH*:*Et*OAc = 2:1); NMR-data are in accordance with those reported in Ref. [25].

General Procedure for the Preparation of Methyl Ethers

TMSCHN_2 (1.0 mmol) was added dropwise to a vigorously stirred solution of the respective alcohol (1 mmol) and *FBA* (1 mmol, 8 *M* in H_2O) in CH_2Cl_2 (15–20 cm^3) at 0°C during 20 min. The yellow colour of *TMS*CHN_2 immediately disappeared with evolution of N_2. Stirring at 0°C was continued,

and three further amounts of *TMS*CHN_2 (0.5 mmol/0.25 mmol/0.25 mmol) were added dropwise with intervals of 20 min. The ice-cooled mixture was stirred for further 30 min, neutralized with Et_3N and concentrated. The residue was redissolved in Et_2O and washed with cold H_2O. After drying (Na_2SO_4) and concentration to dryness the respective methyl ether was purified as described below.

Ethyl {1R-(1α,4aβ,4bα,8aβ,9α,10aα)}-1,2,3,4,4a,4b,5,6,8a,9,10,10a-dodeca-hydro-9-methoxy-1,4a-dimethyl-7-(1-methylethyl)-1-methoxycarbonyl-phenanthrene-9β-yl-acetate (**5a**, $C_{26}H_{42}O_5$)

The product was purified by CC using toluene:*Et*OAc = 3:1 as eluent. Yield 42%; colourless oil; $R_f = 0.57$ (silica, toluene:*Et*OAc = 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.81$ (s, CH_3-18), 0.95 (d, $J = 6.8$ Hz, CH_3-16), 0.96 (d, $J = 6.8$ Hz, CH_3-17), 1.03 (t, $J = \sim 13$ Hz, H-1_{ax}), 1.03–1.14 (m, H-11_{ax}), 1.16 (s, CH_3-19), 1.23 (t, $J = 7.2$ Hz, CH_3-25), 1.37 (d, $J = \sim 13$ Hz, H-6_{eq}), 1.40 (t, $J = \sim 11$ Hz, H-9), 1.50–1.60 (m, H-2_{ax}, H-2_{eq}), 1.52 (d, $J = \sim 12$ Hz, H-3_{eq}), 1.72 (d, $J = \sim 13$ Hz, H-1_{eq}), 1.73 (d, $J = \sim 13$ Hz, H-11_{eq}), 1.73–1.83 (m, H-3_{ax}), 1.85 (t, $J = \sim 13$ Hz, H-6_{ax}), 1.91–1.96 (m, H-12_{ax}, H-12_{eq}), 2.05 (dd, $J = 13.0$, 2.3 Hz, H-5), 2.16 (sept, $J = 6.8$ Hz, H-15), 2.22 (d br, $J = 10.6$ Hz, H-8), 2.53 (d, $J = 13.9$ Hz, H-22), 2.69 (d, $J = 13.9$ Hz, H-22′), 3.05 (s, CH_3-26), 3.60 (s, CH_3-21), 4.11 (qd, $J = 7.2$, 2.8 Hz, H-24, H-24′), 5.39 (s, H-14) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (C-18), 14.2 (C-25), 16.7 (C-19), 18.0 (C-2), 21.3 (C-16*), 21.7 (C-17*), 22.1 (C-11), 26.3 (C-12), 29.7 (C-6), 35.0 (C-15), 36.0 (C-10), 36.9 (C-3), 37.3 (C-1), 40.5 (C-22), 42.2 (C-8), 43.0 (C-5), 47.1 (C-4, C-9), 48.7 (C-26), 51.7 (C-21), 60.3 (C-24), 76.8 (C-7), 118.6 (C-14), 143.6 (C-13), 171.5 (C-23), 179.2 (C-20) ppm; $[\alpha]_D^{26} = -3.3°\ cm^2\ g^{-1}$; ($c = 0.34$, CH_2Cl_2); $[\alpha]_{546}^{26} = -6.5°\ cm^2\ g^{-1}$; ($c = 0.34$, CH_2Cl_2); IR (KBr): $\bar{\nu} = 3436$ (s), 2950 (s), 2924 (w), 1728 (s), 1463 (m), 1177 (s) cm^{-1}; UV (CH_2Cl_2): λ_{max} ($lg\varepsilon$) = 234.0 (2.12) nm; ESI-MS: m/z (%) = 457 (56) $[M + Na]^+$, 403 (38) $[M - CH_3O]^+$, 343 (100); HR-MS: m/z (%) = 452.3345 (100) $[M + NH_4]^+$, calculated for $C_{26}H_{46}NO_5$: 452.3376.

Isoborneol methyl ether (**5b**)

The product was purified by CC using *CH*:*Et*OAc = 5:1 as eluent. Yield 51%; colourless oil; $R_f = 0.64$ (silica, *CH*:*Et*OAc = 5:1); NMR-data are in accordance with those reported in Ref. [26].

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