2-Norbornyldimethylsilyl Ethers (NDMS): A New Protecting Group for Alcohols and Carboxylic Acids

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Abstract: The use of the readily available 2-norbornyldimethylsilyl group (NDMS) in the protection of alcohols and carboxylic acids is described. Stabilities of the corresponding silyl compounds towards various reagents and deprotection conditions are compared with *tert*-butyldimethylsilyl-, *iso*-propyldimethyl and trimethylsilyl groups.

Key words: silicon, protecting groups, ethers, esters, hydrosilylation

The ideal protecting group for an active-hydrogen moiety such as an alcohol or a carboxylic acid should attach in high yield, be stable towards a large number of reaction conditions and, at the same time, be selectively removable in the presence of other functional groups containing different protecting groups. While no single silyl group can fulfill all of these conditions in all cases, the availability of different silyl groups offers an appropriate answer to nearly every protection-deprotection challenge.[1] The range of organic groups available on the silicon atom changes both steric and electronic characteristics of the protecting group and thereby causes different stabilities of the silyl compound to a wide variety of reaction and deprotection conditions. It is this versatility, which allows the synthetic chemist to select a silyl group that can, for example, be selectively removed in the presence of another silyl or other protecting group. The ease and high-yield introduction and deprotection contribute significantly to the popularity and utility of silyl protecting groups.[2]

Some of the most popular silyl groups used in organic synthesis and their relative stability towards acid catalyzed solvolysis are shown below (Table 1).

For applications in the pharmaceutical industry pricing is a further important topic, especially because the silyl group does usually not contribute any atoms to the final target molecule.

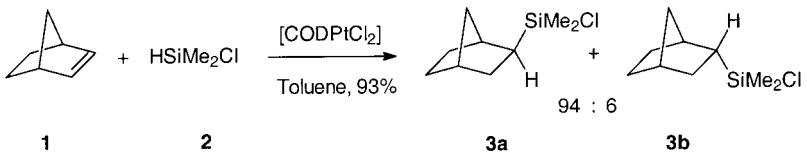
Table 1 Relative Stability of Popular Silyl Protecting Groups[3]

-$SiMe_3$ (TMS)	-$SiMe_2$-*i*-Pr (IPDMS)	-$SiMe_2$-*t*-Bu (TBDMS)	-$SiMe_2$Th (TDS)	-Si*i*Pr3 (TIPS)
1	86	20000	50000	700000

Therefore, low-cost protecting groups like trimethylsilyl are generally favored, if they can fulfill the needs. The preparation of bulkier silyl groups like TBDMS, preferred in the research laboratory owing to their simple NMR spectra and superior stability, involves an organometallic (Grignard or lithium chemistry) reaction step, which makes these reagent much more expensive.[4,5] This is why trimethylsilyl is still by far the most widely used silyl protecting group for large-scale synthesis despite its inferior performance compared with TBDMS.

In order to find a more easily available silyl protecting reagent that retains most of the superior properties of the TBDMS group, we examined the 2-norbornyldimethylsilyl group (NDMS). 2-Norbornyldimethylchloro silane (**3**) can be easily prepared by Pt-catalyzed hydrosilylation of chlorodimethylsilane (**2**) with 2-norbornene (**1**) in high yields.[6] By using [COD]$PtCl_2$ as a catalyst, a 94:6-mixture of exo/endo-isomers **3a**/**3b** is obtained (Scheme 1).[7] This mixture cannot be separated by distillation and is therefore used as it is. Chemical purity is usually >99% (GC). The product is a colorless liquid with bp 120 °C/10 mbar.

The NDMS chlorosilane is capable of masking primary, secondary and tertiary alcohols as well as carboxylic acids by using standard protocols (imidazole or NEt_3 as base, ambient temperature for primary/secondary alcohols).



Scheme 1 Hydrosilylation of norbornene

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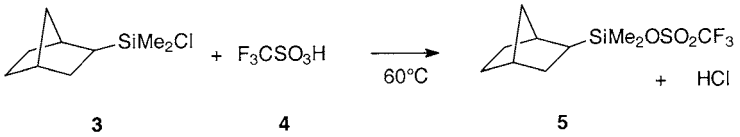


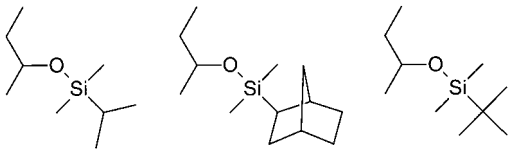
3 4 5

Scheme 2 Synthesis of NDMS-Triflate (94:6 mixture of *exo*/*endo*-isomers).

However, in line with the TBDMS group the introduction of the more sterically demanding NDMS group requires harsher reaction conditions (elevated reaction temperatures, prolonged reaction times) for the formation of NDMS silyl ethers of tertiary alcohols, e.g. NDMS-ether of *tert*-butanol requires 8 h/80 °C using imidazole as base.

Alternatively, we would like to introduce the NDMS silyl triflate **5** as very powerful silylating reagent capable of silylating even tertiary alcohols under mild reaction conditions (2,6 lutidine as base, ambient temperature, 2 h, aqueous work-up). The NDMS silyl triflate can be simply prepared by reacting neat NDMS silyl chloride **3** with triflic acid **4** at 60 °C for 10 h (Scheme 2). The triflate is a colorless liquid that can be purified by direct distillation (bp 100–105 °C/1 mbar) from the reaction flask in 83% yield. The transformation from chloride to triflate does not alter the *exo*/*endo*-ratio according to GC/NMR.

Table 2 $T_{1/2}$ for Cleavage of the Si-O-Bond in Silyl Ethers



6 7 8

Reagent	2-Propyl [IPDMS]	2-Norbornyl [NDMS]	*tert*-Butyl [TBDMS]
2 M BuMgCl in THF	stable	stable	stable
n-BuLi in hexane/THF	stable	stable	stable
$LiAlH_4$ in THF	stable	stable	stable
PCC in CH_2Cl_2	1 h	2 h	stable
0.05 M NaOH in MeOH	stable	stable	stable
KF in MeOH (25 °C)	stable	stable	stable
KF in MeOH (65 °C)	2 h	7 h	stable
n-Bu_4NF in THF	<< 1min	< 1min	> 30 min

In order to determine suitable deprotection conditions silyl ethers of *n*-butanol, 2-butanol, cyclohexanol, *tert*-butanol and phenol were synthesized.[8] Table 2 shows various reaction and cleavage conditions that are commonly used in desilylation reactions for secondary alcohols. The progress of the reaction was analyzed using GC techniques and compared to a blank sample. For direct comparison, the corresponding silylethers of IPDMS **6** and TBDMS **8** were treated in the same way as the NDMS silyl ether **7**.

All three silyl ethers withstand organometallic reagents (entries 1–3) without any noticeable decomposition. Strong oxidizing agents like pyridine chlorochromate (entry 4) cause slow decomposition of IPDMS and NDMS, but show almost no effect on TBDMS. All three protection groups are stable towards alkaline hydrolysis at room temperature. Potassium fluoride in methanol does not cause deprotection at ambient temperature. However, at reflux slow deprotection can be seen. The rate of IPDMS-deprotection with potassium fluoride is about 2–3 times faster than the NDMS-deprotection. Both secondary alkyl silyl groups are cleaved rapidly by tetrabutylammonium fluoride in THF, whereas the deprotection of TBDMS takes some hours ($t_{1/2} \approx 0.5$ h).

The progress of the acid-catalyzed hydrolysis was followed by GC over an appropriate period of time. As an example, Figures 1 and 2 show the acid hydrolysis of a primary and a secondary alcohol protected by TMS, IPDMS, NDMS, TBDMS. The NDMS-ethers are cleaved 2 to 3 times more slowly than the IPDMS ether under otherwise identical conditions. Despite its steric bulk, the secondary alkyl residue does not reach the stability of a tertiary alkyl group (TBDMS). Therefore, the NDMS-silyl group is always the choice if the protecting group has to withstand an aqueous work-up, which is often difficult with the TMS group, and strong resistance to dilute acids is not needed or even prohibitive.

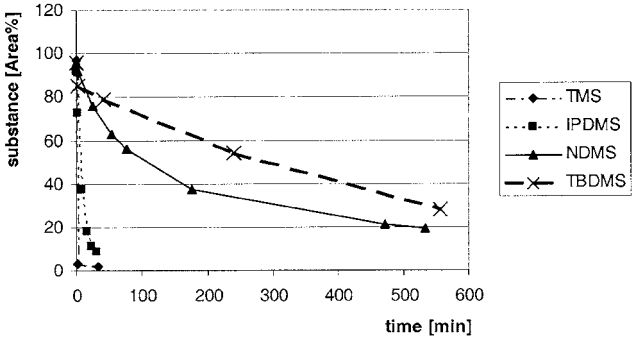
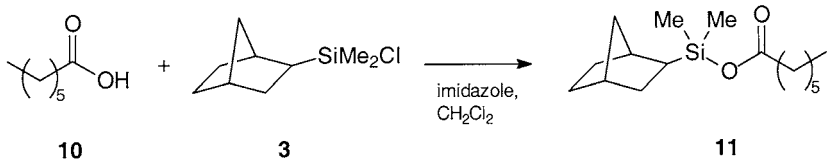


Figure 1 Acid-catalyzed hydrolysis of silyl-protected 1-butanol



10 **3** **11**

Scheme 3 Preparation of silyl esters.

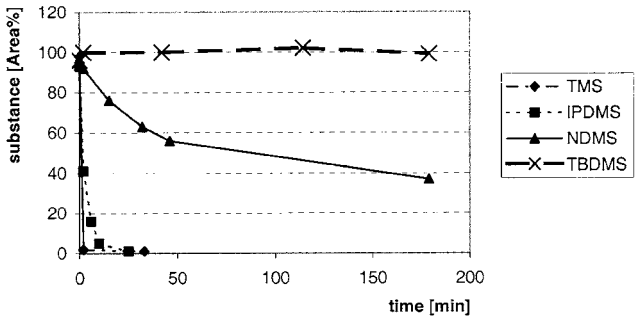


Figure 2 Acid-catalyzed hydrolysis of silyl-protected 2-butanol

As an example for further applications a silyl ester **11** from NDMS silyl chloride and heptanoic acid (**10**) was also prepared (Scheme 3). The NDMS-ester of the carboxylic acid withstands aqueous work-up conditions without deprotection whereas the corresponding TMS-ester suffers quantitative hydrolysis.

In summary, several advantages can be envisioned for the use of the NDMS silyl group as hydroxy protecting moiety: (1) it is readily available at low cost from bulk chemicals, (2) its significantly improved stability compared with trimethylsilyl, exceeding isopropyldimethylsilyl and almost reaching *tert*-butyldimethylsilyl, (3) improved ease of handling as a liquid compared with the solid *tert*-butyldimethylchlorosilane.

2-Norbornyldimethylsilyl Triflate (5)

Triflic acid (7.50 g, 49.0 mmol) is added dropwise to 2-norbornyldimethylchlorosilane (9.50 g, 49.3 mmol) at ambient temperature. The reaction mixture is stirred at 60 °C for 10 h (Attention: liberation of gaseous HCl). The reaction mixture is subjected to fractional distillation providing **5** as a colorless liquid (12.3 g, 83%, bp 100–105 °C/1 mbar), again as a mixture of *exo*/*endo*-isomers (GC, same ratio 94:6 in favor of the exo-isomer). ^{1}H NMR (300 MHz, $CDCl_3$), major isomer: δ = 0.45 (2 s, 6 H), 0.93 (t, 1 H), 1.10–1.40 (m, 4 H), 1.50 (d, 2 H), 1.60 (d, 2 H), 2.35 (s, 2 H); minor isomer: only δ = 0.52 [s, $Si(CH_3)_2$] is sufficiently separated from the major isomer. Purity 93% (GC, sum of *exo*/*endo*-isomers). Major impurity was 1,1,3,3-tetramethyl-1,3-dinorbornyl-disiloxane (5%, hydrolysis of the product). The product can be used for silylations without any further purification.

References

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; J. Wiley & Sons: New York, **1999**. (b) Kocieński, P. J. *Protecting Groups*; Thieme: Stuttgart, **1994**.

(2) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817.

(3) van Look, G.; Simchen, G.; Heberle, J. *Silylating Agents*; Fluka Chemie AG: Buchs, **1995**.

(4) (a) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190. (b) Morrison, R. J.; Hall, R. W.; Dover, B. T.; Kamienski, C. W.; Engel, J. F. Eur. Pat. EP 525 880, **1998**; *Chem. Abstr*. **1993**, *118*, 192001. (c) Shirahata, A. Eur. Pat. 405 560, **1998**; *Chem. Abstr*. **1991**, *114*, 164495. (d) Winterfeld, J.; Abele, B. C.; Stenzel, O. PCT-WO 2000/64909, **2000**; *Chem. Abstr*. **2000**, *132*, 279350.

(5) An exemption is the $AlCl_3$-catalyzed hydrosilylation of 2,3-dimethyl-2-butene with dimethylchlorosilane leading to thexyldimethylchlorosilane: Oertle, K.; Wetter, H. *Tetrahedron Lett*. **1985**, *26*, 5511.

(6) (a) Eddy, V. J.; Hallgren, J. E. *J. Org. Chem.* **1987**, *52*, 1903. (b) Green, M.; Spencer, J. L.; Stone, F. G. A.; Tsipsis, C. A. *J. Chem. Soc., Dalton Trans*. **1977**, 1519.

(7) Depending on the catalyst batch, ratios of 93:7 up to 95:5 were obtained. Major isomer is **3a**(*exo*) according to citation 6.

(8) All silylethers are *exo*/*endo*-mixtures with the same ratio as the silylating agent used. The isomers can be distinguished by the different chemical shifts of the methyl groups on the silyl atom in the ^{1}H NMR spectra. However, the more preferable method of analysis is ^{29}Si NMR spectroscopy providing only two well-distinguished signals, e.g. Dimethyl-(2-norbornyl)-phenoxy silane: ^{1}H NMR (300 MHz, $CDCl_3$), major isomer: δ = 0.12 (2s, 6 H), 0.70 (t, 1 H), 1.10–1.5 (m, 8 H), 2.12–2.30 (m, 2 H), 6.70–6.80, 6.82–6.90, 7.09–7.20 (Phenyl, 5 H); minor isomer: δ = 0.20 [$Si(CH_3)_2$, 6 H]. ^{29}Si NMR (99 MHz, $CDCl_3$), major isomer: δ = +17.6; minor isomer: δ = + 19.6 ppm. Analysis by GC providing the same ratio is also possible.