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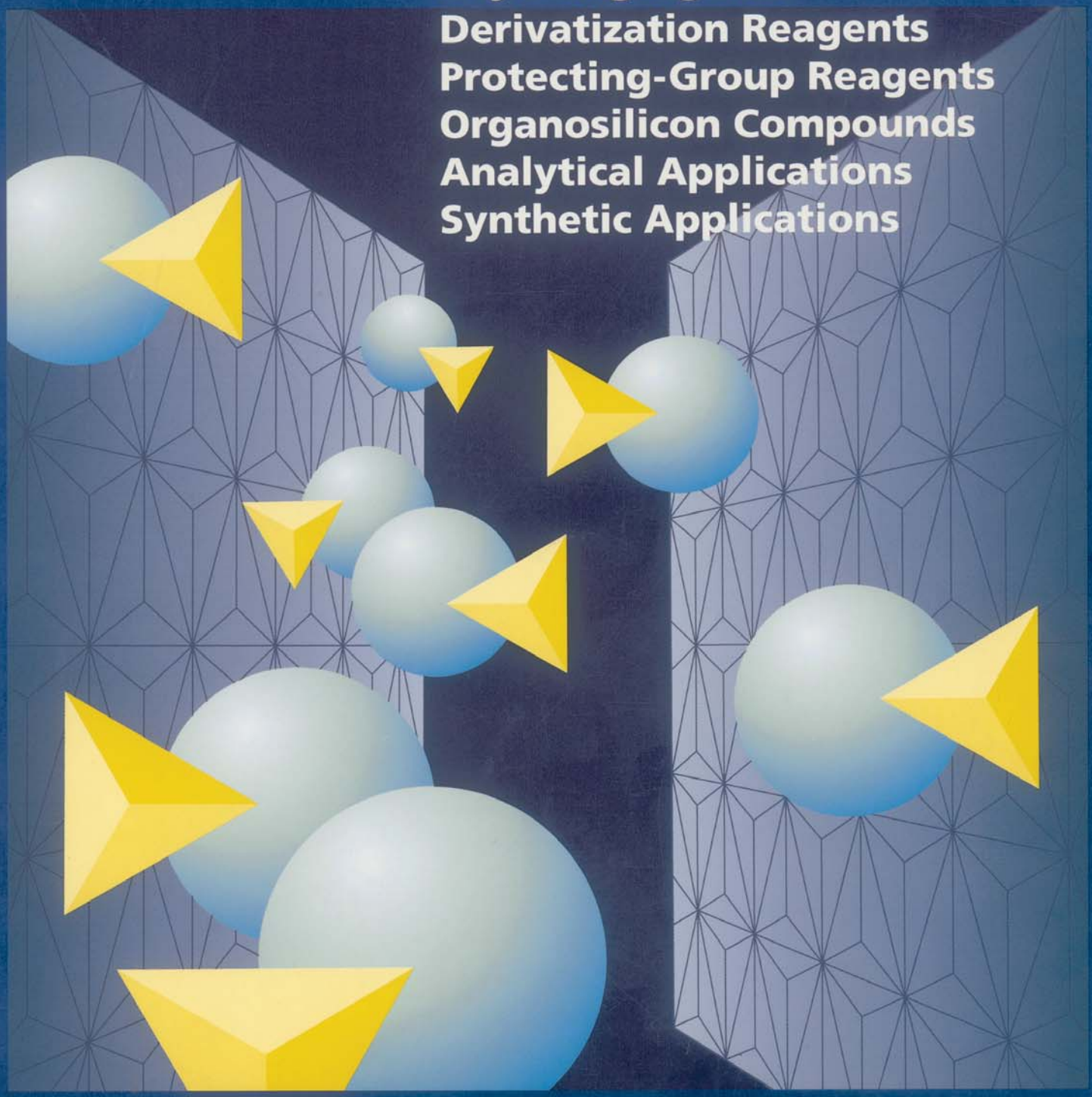
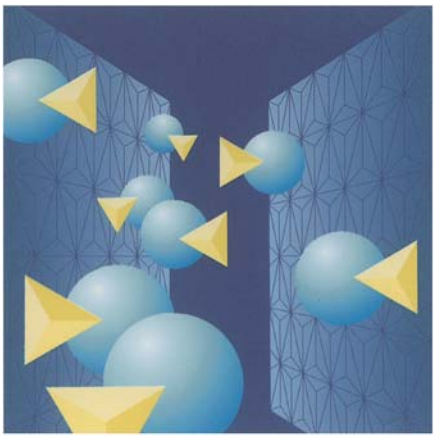
Chemika

Silylating Agents
Derivatization Reagents
Protecting-Group Reagents
Organosilicon Compounds
Analytical Applications
Synthetic Applications





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We hope that you will take advantage of this brochure in your daily work with silylating agents and their applications in research and development as well as in production.

Silylating Agents

Derivatization Reagents
Protecting-Group Reagents
Organosilicon Compounds
Analytical Applications
Synthetic Applications

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ISBN 3-905617-07-2

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van Look, Gert, Dr.:
Silylating Agents
by Gert van Look
Buchs: Fluka Chemie AG
(1988)

Simchen, Gerhard, Prof. Dr.:
Silylating Agents
Second Edition
(1995)

Heberle, Jochen, Dipl. Chem.:
Silylating Agents
Second Edition
(1995)

Preface

The field of organosilicon chemistry has undergone explosive growth in the past thirty years, and many reviews and monographs have appeared covering different topics. Nevertheless, due to the rapidly increasing volume of literature, there is always a necessity for up-to-date reviews.

The silylation of organic compounds for synthetic and analytical purposes, an important part of organosilicon chemistry, is the subject matter of this totally revised and enlarged monograph.

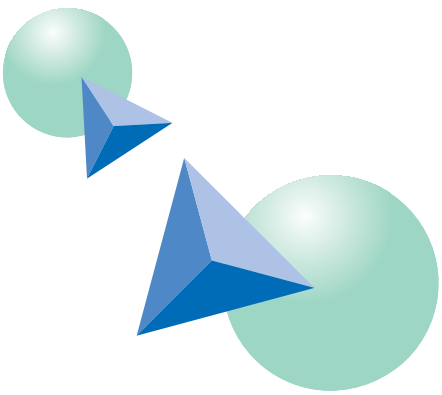
The term "silylation" is defined as the substitution of a hydrogen atom bound to a hetero atom (–OH, =NH, –SH) by a silyl group, forming a silicon hetero atom bond, without any further alteration of the molecule. Excluded from this review are therefore the silylation of carbon atoms, hydrosilylation, cleavage reactions etc., as well as the introduction of silicon-containing protecting groups which does not involve the formation of a silicon hetero atom bond. Silylation of the surface of organic and inorganic material (as glass, silica etc.) is likewise excluded from this treatise but some references are mentioned in special cases.

The monograph describes the different silyl groups and the reagents available from Fluka for their introduction. Due to the comprehensive program of organosilicon compounds available from Fluka, including many exclusive specialities, all of the major and most of the special silyl groups and silylating agents are mentioned. Hence this treatise represents an almost comprehensive compilation of current information on the subject. All literature till the end of 1986 was taken into consideration and in some cases references from 1987 are cited. References from the primary literature are given for the important and the more recent publications, and for those papers which are not cited in the secondary literature. In all other cases reviews or leading references are cited.

My apology in advance for any omissions and errors, which are unavoidable in a work of this nature.

I would like to express my gratitude to Miss Irene Singer for preparing the typescript, to Mrs. Joan Forrer for correcting the manuscript, to Dr. Jörg Widmer for assistance in literature research and to Prof. Dr. Gerhard Simchen for helpful suggestions. Last but not least, my grateful thanks are due to Dr. Walter Graf for proposals and critical discussion and for his engagement in the technical realisation of this monograph.

Gert van Look
Fluka Chemie AG



Second Edition

There have been numerous important developments in synthetical and analytical application since the first edition of "Silylating Agents" was published. Thus we decided to revise the first edition thoroughly and to bring it up to date. All literature till the end of 1993 was taken into consideration and in some cases references from 1994 are cited.

Among the more notable developments are 2-(trimethylsilyl)ethanol and 2-(trimethylsilyl)ethoxymethylene chloride protecting groups, but many others containing silicon have been included as well.

Methods for carbosilylation are described for some silylating agents.

After the description of silylating and protecting agents, we have added typical procedures for protection of the more important silylating agents.

The preparative user of this brochure can find a summary of most of the functional groups and their application in the final chapter. Now, it is easier to select the best protecting group for each functional group.

The chapter "Silanisation" gives a short list of reagents, which can be used for surfaces like glass or silica gel, used for example in material sciences or in sealing techniques. Although dealing in principle with silylation-processes, silanisation reactions are not used normally for analytical or preparative applications in synthetic chemistry. We have therefore excluded this topic from a broader discussion in this brochure.

We wish to thank Dr. H. Schlemper and Mrs. J. Forrer for their exceedingly helpful assistance, also, Dr. M. Metzulat for his detailed review of new published papers.

J. Heberle
Prof. Dr. G. Simchen

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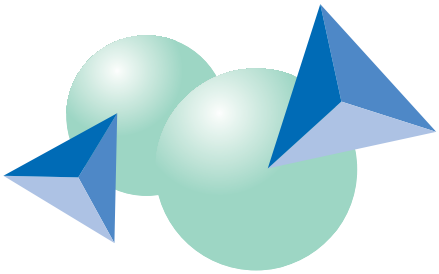

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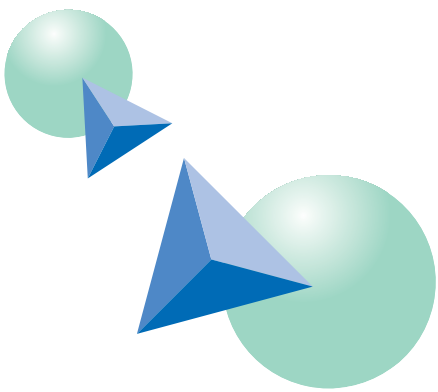
Abbreviations

ADMCS	Allyldimethylchlorosilane
ADMS	Allyldimethylsilyl-
Benzostabase	1,2-Bis(dimethylsilyl)benzene
BMDMCS	Bromomethyldimethylchlorosilane
BMDMS	Bromomethyldimethylsilyl-
BSA	N,O-Bis(trimethylsilyl)acetamide
BSC	N,O-Bis(trimethylsilyl)carbamate
BSF	N, N-Bis(trimethylsilyl)formamide
BSS	Bis(trimethylsilyl) sulfate
BSTFA	N,O-Bis(trimethylsilyl)trifluoroacetamide
BSU	N,N'-Bis(trimethylsilyl)urea
CMDMCS	(Chloromethyl)dimethylchlorosilane
CMDMS	(Chloromethyl)dimethylsilyl-
CMTMDS	1,3-Bis(chloromethyl)-1,1,3,3-tetramethyldisilazane
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMF	N,N-Dimethylformamide
DMIPS	Dimethylisopropylsilyl-
DMIPSCI	Dimethylisopropylchlorosilane
DMPS	Dimethylphenylsilyl-
DMPSCI	Dimethylphenylchlorosilane
DMS	Dimethylsilyl-
DMSO	Dimethylsulfoxide
DPMS	Diphenylmethylsilyl-
DPMSCI	Diphenylmethylchlorosilane
DPTMDS	1,3-Diphenyl-1,1,3,3-tetramethyldisilazane
DTBS	Di-tert-butylsilylene-
ECD	Electron capture detector
Et-DADS	Diethylaminodimethylsilyl-
ETSA	Ethyl trimethylsilylacetate
FID	Flame ionisation detector
Flophemesyl	Pentafluorophenyldimethylsilyl-
GC	Gas chromatography
HMDS	Hexamethyldisilazane
HMDSO	Hexamethyldisiloxane
HMPA	Hexamethylphosphoramide
HPLC	High performance liquid chromatography
IPOTMS	Isopropenyloxy-trimethylsilane
LDA	Lithium diisopropylamide
Me-DADS	Dimethylaminodimethylsilyl-
MS	Mass spectrometry
MSA	N-Methyl-N-trimethylsilylacetamide
MSHFBA	N-Methyl-N-trimethylsilylheptafluorobutyramide
MSTFA	N-Methyl-N-trimethylsilyltrifluoroacetamide
MTBSTFA	N-tert-Butyldimethylsilyl-N-methyltrifluoroacetamide
Nonaflate	Perfluoro-1-butanesulfonate
SEM	2-(Trimethylsilyl)ethoxymethyl-



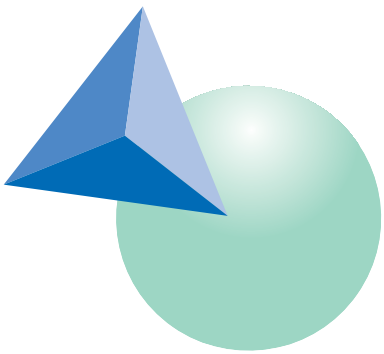
SEM-Cl	2-(Trimethylsilyl)ethoxymethyl chloride
Stabase	1,1,4,4-Tetramethyl-disilethylene-1,4-diyl-
TBAF	Tetrabutylammonium fluoride Trihydrate
TBDMS	tert-Butyldimethylsilyl-
TBDMSacac	4-tert-Butyldimethylsiloxy-3-penten-2-one
TBDMSCl	tert-Butyldimethylchlorosilane
TBDMSIM	1-(tert-Butyldimethylsilyl)imidazole
TBDMS-OTf	tert-Butyldimethylsilyl triflate
TBDPS	tert-Butyldiphenylsilyl-
TBDPSCl	tert-Butyldiphenylchlorosilane
TBMPSi	tert-Butyl-methoxy-phenylsilyl-
TBMPSiBr	tert-Butyl-methoxy-phenylbromosilane
TDS	Thexyldimethylsilyl-
TDSCl	Thexyldimethylchlorosilane
TEOC	2-(Trimethylsilyl)ethoxycarbonyl
TEOC-ONp	2-(Trimethylsilyl)ethyl p-nitrophenyl carbonate
TES	Triethylsilyl-
TESCl	Triethylchlorosilane
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPDS	1,1,3,3-Tetraisopropyldisiloxane-1,3-diyl-
TIPDSCl2	1,3-Dichloro-1,1,3,3-tetraisopropyldisiloxane
TIPS	Triisopropylsilyl-
TIPSCl	Triisopropylchlorosilane
TLC	Thin layer chromatography
TMBS	Trimethylbromosilane
TMCS	Trimethylchlorosilane
TMDS	1,1,3,3-Tetramethyldisilazane
TMIS	Trimethyliodosilane
TMS	Trimethylsilyl-
TMSA	Trimethylsilylacetamide
TMSacac	4-Trimethylsiloxy-3-penten-2-one
TMSCN	Trimethylsilyl cyanide
TMSDEA	N-Trimethylsilyldiethylamine
TMSDMA	N-Trimethylsilyldimethylamine
TMSEt	2-Trimethylsilylethyl-
TMSEtOH	2-Trimethylsilylethanol
TMSIM	1-(Trimethylsilyl)imidazole
TMS nonaflate	Trimethylsilyl perfluoro-1-butanesulfonate
TMSO	3-Trimethylsilyl-2-oxazolidinone
TMS-OTf	Trimethylsilyl triflate
TPDMDS	1,1,3,3-Tetraphenyl-1,3-dimethyldisilazane
TPS	Triphenylsilyl-
TPSA	Triphenylsilylamine
Triflate	Trifluoromethanesulfonate

1. Introduction

Silylation is an important tool in both analytical and synthetic chemistry. Generally all hetero atoms containing active hydrogens, as well as enolisable carbonyl compounds can be silylated (the silylation of carbon atoms is not discussed here).

In analytical chemistry, silylation has been used since the late fifties in gas chromatography and mass spectrometry, for the derivatisation of a wide variety of products and functional groups. Silylation of a polar compound results in reduced polarity, enhanced volatility and increased thermal stability, and enables the GC-MS analysis of many compounds otherwise involatile or too unstable for these techniques. The trimethylsilyl group is the most popular and versatile silyl group for these purposes, and a variety of trimethylsilylating agents with different properties (concerning e.g. volatility, silylation by-products, reactivity, selectivity etc.) has been developed. Nevertheless other silyl groups have become more and more important in the last twenty years. Their use often enables better GC separation and the application of special detection techniques. In mass spectrometry they often produce more diagnostic fragments with more abundant ions. The enhanced stability to hydrolysis of the sterically crowded trialkylsilyl groups allows easier handling of the derivatives thus enabling the application of some in HPLC.

In synthetic organic chemistry, trialkylsilyl groups are widely employed to protect mainly the hydroxyl group. However most of the other functional groups can be protected as well. Silyl enol ethers and silyl ketene acetals are highly useful, reactive, synthetic intermediates. The trimethylsilyl moiety is the silyl group originally used and is even today of prime importance, e.g. for the preparation of silyl enol ethers, silyl ketene acetals and particularly for the synthesis of nucleosides and nucleotides. Since the introduction of the sterically more crowded trialkylsilyl groups, silyl protection has become more and more important. The enhanced selectivities in introduction and the different stabilities in cleavage resulted in a veritable boom of applications. Today, in practically every total synthesis, a silyl protecting group is employed in some intermediate step. The introduction of cyclic silylene or bifunctional silyl protecting groups has further enlarged the technique of silyl protection.



2. Comparison of the Stability of the Different Trialkylsilyl Protecting Groups

The wide stability range of the different trialkylsilyl groups to basic and acidic hydrolysis as well as in fluoride ion-mediated cleavage accounts for the ever increasing use of these protecting groups in organic synthesis. The appropriate choice of the three ligands attached to the silicon atom can therefore provide a tailor-made protecting group of stability relevant to the reaction conditions to be applied.

The stability of a compound $R^1R^2R^3SiX$ towards solvolysis of the Si-X bond and towards other chemical reactions depends on the nature of R^1, R^2, R^3 and on X. Although the aim of this chapter is to analyse the influence of the ligands attached to silicon (R^1, R^2, R^3) on the stability of a trialkylsilyl protected compound, the influence of X will be discussed briefly.

Table 2.1
Average Bond Energies of Si-X (kcal/mole) [1]

SiF	142
Si-O	112
Si-Cl	93
Si-N	75-80
Si-Br	76
Si-H	70
Si-C	69
Si-Si	68
Si-I	59
Si-S	54

Table 2.2
Relative Electronegativity (non-empirical scale) [2]

F	4.0
O	3.52
N	3.16
Cl	2.84
H	2.79
Br	2.52
S	2.52
Se	2.4
C	2.35
P	2.11
Si	1.64

The influence of X on the solvolytic stability of $R^1R^2R^3SiX$ can be explained on the basis of the bond energies of the Si-X bond (see table 2.1), the polarisation of the Si-X bond (depending on the electronegativity (see table 2.2) of the atom bonded to silicon, and its substituents) and on the steric bulk of X. From these facts some general rules can be stated:

- the stability of R_3SiX decreases normally in the order (along decreasing bond energies): $R_3Si0- > R_3SiN= > R_3SiS-$
- silicon is generally more electropositive than X, thus nucleophilic attack occurs normally at silicon and electrophilic attack at X. The stability of a TMS ether Me_3SiOR to acidic hydrolysis is therefore increased and to basic hydrolysis decreased when R is an electron-withdrawing group and vice versa (when R is an electron-donating group) [3, 4]
- steric bulk of X enhances the stability to both acidic and basic hydrolysis [3, 4].

Most studies on the influence of the ligands at silicon on the stability to hydrolysis of $R^1R^2R^3SiX$ have been undertaken with trialkylsilylethers of alcohols or phenols. Similar to the influence on stability of ligand X, as stated above, the following general rules have been found:

- the more bulky R^1, R^2 and R^3, the higher the stability of the silyl ether to both acidic and basic hydrolysis [3–6],
- electron-withdrawing groups increase the stability to acidic hydrolysis and decrease the stability to basic hydrolysis and vice versa (for electron-donating groups) [3–5].

Thus if one or more of the ligands at silicon are phenyl groups, a differentiated reactivity to acidic or basic hydrolysis can be found: under acidic conditions, steric and electronic effects both decelerate the rate of hydrolysis (the Ph_3Si-group is about 400 times more stable than the Me_3Si-group), whereas under basic conditions, steric and electronic effects oppose one another (stability of $Ph_3Si \approx Me_3Si$) [3–5].

The order of stability to acid and base catalysed solvolysis derived from different kinetic measurements is given in tables 2.3 and 2.4 [approximative relative rate factors (TMS=1) as shown]. The different origins of some of the rate factors (measured with different substrates under different conditions), urge cautious consideration of the quantitative data.

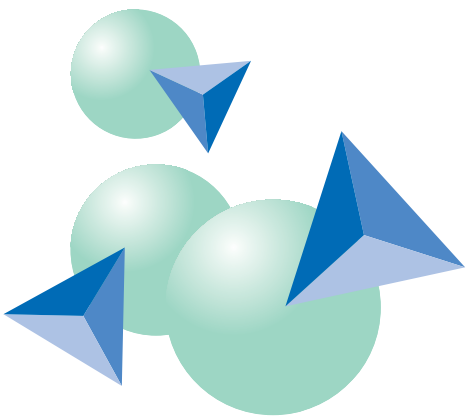


Table 2.3
Relative stabilities ($1/k_{rel}$) of $R^1R^2R^3iOR^4$ (R^4 = menthyl) towards acid-catalysed solvolysis [3]

The exact position of the groups in parantheses cannot be defined reliably due to lack of published data.

Table 2.4
Relative stabilities ($1/k_{rel}$) of $R^1R^2R^3SiOR^4$ (R^4 = menthyl) towards base-catalysed solvolysis [3]

The exact position of the groups in parantheses cannot be defined reliably due to lack of published data.
The position of the trityldimethylsilyl and the tert-butyl-methoxy-phenylsilyl group (mentioned in table 2.3) cannot be defined in table 2.4 from the results published.
The former is known to be relatively unstable to basic hydrolysis, the latter, which has good stability to basic hydrolysis, may be somewhat less stable than the TBDMS and TBDPS group.

Only very little quantitative data are available [9, 11] on the stability of the different trialkylsilyl ethers towards fluoride-based reagents. Nevertheless it can be proposed that the order of cleavage with the basic fluoride reagents (e. g. tetrabutylammonium fluoride trihydrate) is similar to that found for basic hydrolysis.
In the case of the slightly acidic fluoride-based reagents such as HF/acetonitrile or BF_3 etherate, the sequence of stability and the rate of cleavage of the silyl ethers may tend to be more like those associated with acidic hydrolysis. For example it has been found that a tert-butyl-methoxy-phenylsilyl ether is more stable to acidic hydrolysis than a TBDMS ether, but the former is much more susceptible to cleavage with tetrabutylammonium fluoride [10] (for basic hydrolysis no comparative data have been published).

The stability of the different trialkylsilyl derivatives to other chemical reactions such as metal organic reactions, oxidation, reduction and to liquid chromatography, normally increases in the same sequence as given for acidic hydrolysis. Nevertheless the replacement of one or two methyl groups of the TMS moiety by phenyl ligands – which increases the stability to acidic hydrolysis to a small extent only [3, 5] – results in a remarkably higher stability to many reaction conditions, including those of liquid chromatography (as shown for dimethylphenylsilyl ethers [16] and diphenylmethylsilyl ethers [5]).

In addition it has been shown that silyl esters protect acids against reduction with hydroborating agents [17].

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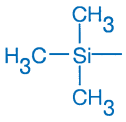
3. Reagents for the Introduction of the Trimethylsilyl Group

Contents: page



3.1 The Trimethylsilyl Group, TMS Group

The TMS group is the silyl group originally used for protection and derivatisation of all kinds of functional groups and even today it is still the most important [1–9].

In gas chromatography and mass spectrometry, this is the silyl group of choice in most cases, combining thermal and chemical stability with high volatility (only dimethylsilyl derivatives are more volatile, but much less stable) [1–3].

In synthetic chemistry the TMS group is widely used as protecting group [5, 8, 9] particularly for hydroxyl groups [4, 5, 8, 9, 25], enolisable carbonyl compounds [4, 8, 10] and in nucleoside and nucleotide synthesis [8, 11]. It can be introduced easily and selectively by choosing the appropriate trimethylsilylating reagent, and is stable under a wide range of reaction conditions. A severe drawback is its tendency to hydrolysis which prevents chromatography on silica gel in most cases. This sensitivity necessitates the handling of derivatives, other than TMS ethers, under exclusion of moisture.

Because of this moisture sensitivity, cleavage of TMS derivatives can be achieved very simply by acidic or basic hydrolysis or solvolysis with an alcohol (mainly methanol or ethanol) [5, 8, 9, 14]. The rate of hydrolysis decreases normally in the sequence R_2NTMS > RCOOTMS > ROTMS. Silyl enol ethers are generally more easily hydrolysed than normal silyl ethers. The rate of hydrolysis of TMS ethers depends on both steric and electronic effects: an increasing steric size of the alcoholic part decreases the rate of both acidic and basic hydrolysis, whereas an electron-withdrawing group increases only the rate of basic hydrolysis, and decreases the rate of acidic hydrolysis [12]. Thus it is possible to cleave a TMS ether of a primary alcohol without affecting TMS ethers of secondary and tertiary alcohols [5, 8]. It is even possible to cleave an alcoholic TMS ether selectively in the presence of a phenolic one by ethanolysis catalysed with a carboxylate resin (H^+ form) [13]. On the other hand, a phenolic TMS ether can be cleaved without affecting alcoholic TMS ethers by ethanolysis catalysed with a quaternary ammonium resin in the OH^- form [13].

TMS ethers can also be cleaved very conveniently and selectively with fluoride ions (compare 4.3, on the cleavage of the TBDMS group and references given therein). Common sources of fluoride ions are tetrabutylammonium fluoride [5, 8], potassium fluoride in DMF [5, 8, 14], triethylamine hydrofluoride in pyridine [15] and HF in methanol or acetonitrile [5, 8]. Using these methods, the TMS group can often be removed selectively in the presence of other more bulky trialkylsilyl groups.

TMS derivatives can also be transformed directly into other functionalities: for example oxidation of TMS ethers of secondary alcohols with trityl tetrafluoroborate [16, 17] or N-bromosuccinimide [18] leads directly to ketones, the trimethylsiloxy group can be replaced by a hydrogen by treating with lithium aluminum hydride/aluminum chloride in ether [18]. Reaction of a TMS ether with a carboxylic acid anhydride in pyridine catalysed by HF or BF_3 etherate leads directly to the corresponding ester [14], which in turn can be transformed directly into carboxylic acid bromides by reaction with triphenylphosphine dibromide [24].

Principally, every compound containing a TMS group bound to a hetero atom, and even some compounds with the TMS group attached to a carbon atom, can act as trimethyl silylating agent. A variety of trimethyl silylating reagents of different reactivities has been prepared and used in analytical and synthetic chemistry. The sequence of reactivity of the most common trimethyl silylating agents to hydroxyl groups is generally as follows: TMCS < HMDS < TMCS/base < HMDS < TMCS < TMSDEA and TMSDMA < TMS amides < TMSIM [1]. For the conversion of ketones to enol ethers, the following order of reactivity has been found: TMCS < TMS methanesulfonate < TMS benzenesulfonate < BSS < TMBS < TMS triflate < TMIS (in 1,2-dichloroethane with triethylamine as base) [19]. The silylation rate of different functional groups decreases normally in the sequence ROH > ArOH > RCOOH > RNH_2 > RSH. Steric factors can drastically alter this series. Additional comparative data on the silylation potential of the different reagents can be found in the reagent sections.

Most of the trimethylsilylating reagents described in the literature are available from Fluka and thus abstracted in this brochure in the corresponding sections. Also, the silylating mixtures HMDS/TMCS 2:1, BSA/TMSIM /TMCS 3:3:2 (v/v/v), BSTFA/TMSIM/TMCS 3:3:2 (v/v/v), BSA containing 5% TMCS, BSTFA containing 1% TMCS, and MTBSTFA with 1% TBDMSCl are avilable from Fluka.

Further interesting trimethylsilylating reagents not yet in the Fluka-programme and not described here in detail are: N,O-bis(trimethylsilyl)sulfamate [20], 1-methoxy-1-trimethylsiloxypropene [21], N-trimethylsilyl N,N′ diphenylurea [6], Nafion®-TMS (a polymer supported perfluorinated sulfonic acid trimethylsilylester) [22], N-trimethylsilyl-pyrrolidine [23], and N-trimethylsilyl-piperidine [23].

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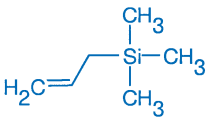

3.1.1 Allyltrimethylsilane

Allyltrimethylsilane, a highly versatile synthetic reagent [1,2] can be used for silylating alcohols and carboxylic acids, as described by T. Morita et al. [3] in 1980 and for thiols. The silylated derivatives are formed in acetonitrile when an acid catalyst, such as p-toluenesulfonic acid is present. The products are quantitatively formed and propene is the only gaseous by-product. Other common catalysts for the silylation are I_2 [4], Br_2 [4], TMIS [4], TMBS [4], CF_3SO_3H [5], Nafion®-H [6], described by A. Hosomi and H. Sakurai [4] and by G. A. Olah and co-workers [5, 6].

Protection of aliphatic hydroxy compounds has been described using carried clay as a catalyst [8]. 1,1-Dihydroxy compounds have been silylated with allyltrimethylsilane and TMS triflate as a catalyst by M. Yalpani and G. Wilke [7].

Mercaptans and thiophenols can be silylated with CF_3SO_3H as catalyst [5].

To silylate enolisable ketones, equimolar amounts of allyltrimethylsilane, CF_3SO_3H and an excess of Et_3N are required to form the silyl enol ether [5].

$TMSOSO_2F$ can be prepared in situ, by treatment of allyltrimethylsilane with FSO_3H. The product, trimethylsilylfluorosulfonate, is an alternative reagent to TMS triflate as a source of Me_3Si^+ [20].

Allyltrimethylsilane is also used to introduce the 2-propenyl substituent (allyl) into a compound, in which O-alkyl [9, 10], O-acyl [11] or hydroxy substituents [12] are removed, e.g. in acetals [21]. Lewis acids such as $BF_3.OEt_2$, $TiCl_4$, $SbCl_5$, $SnCl_4$, are catalysts for this kind of reaction. By using $BF_3.OEt_2$ as catalyst only O-methyl is removed. Tos-O and TBS-O are stable under these conditions [12]. A novel catalyst, trimethylsilyl bis(fluorosulfonyl)-imide, was used by S. Trehan and co-workers [21], and was shown to be more effective than TMS triflate.

The intramolecular addition of allylsilanes to conjugated dienones for the effective construction of five and seven membered rings is described in [13].

Allylic alcohols are formed from aldehydes or acylsilanes [14]. With Lewis acids as catalysts, aldehydes are transformed into allylic alcohols [15, 16].

3-Substituted trimethylallylsilanes have been prepared by the reaction of allyltrimethylsilane with electrophiles such as an oxirane-ring. [17].

Synthesis of 1-substituted ribofuranosides was stereoselectively carried out with a mixture of $SnCl_4/Sn(OTf)_2/LiClO_4$ as a new catalyst system. The treatment of allyltrimethylsilane with 1-acetylribofuranosides and with the catalyst system in different proportions gives different yields of the 1-substituted allyl product [11].

A. Kraus and D. Bougie [18] described the addition of allyltrimethylsilane to an α-β unsaturated ketone with $TiCl_4$ as a catalyst. The product is a 3-allylic ketone. The silylating agent catalysed addition of allyltrimethylsilane to aldehydes has been described [19].

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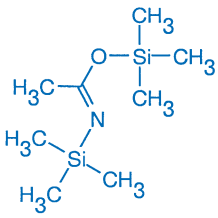

3.1.2. N,O-Bis(trimethylsilyl)acetamide, BSA

BSA, first prepared by L. Birkofer and co-workers [1], is one of the most potent and commonly used silylating agents, particularly for analytical purposes [2, 3, 4, 5]. The silylating potential [2, 6, 7] is similar to that of BSTFA and MSTFA and more potent than HMDS or TMSDEA, depending on the conditions and substrates used. J. F. Klebe and co-workers [8] were the first to use BSA as a silylating agent for different classes of compounds. Depending on the substrate and conditions, BSA transfers one or both TMS-groups, yielding N-TMS-acetamide or acetamide as reaction by-products, which are sufficiently volatile to cause no interference in most gas chromatographic separations.

Analytical applications

BSA can be used for the silylation of all kinds of acidic functional groups, i. e. for alcohols, enols (especially for the ready silylation of non-sterically hindered alcohols), amines, amides, carboxylic acids, amino acids, phenols, steroids, biogenic amines, alkaloids, phosphites and thiols [2, 3, 4, 5, 67, 76]. Because of its low price (it is the cheapest of the silylamides) and its high silylation potential [6, 7], it has become one of the most commonly used silylating agents. Its silylating potential can be increased by choosing an appropriate solvent (e. g. pyridine, DMF, acetonitrile) [3, 8, 28, 36] or by adding a catalyst, usually 1–20 % TMCS [9–16, 26]. A mixture of BSA with 5 % TMCS is available from Fluka (see the section on silylating mixtures).

Other useful catalysts are oxalic acid (for gibberellins and abscisic acid) [16], trifluoracetic acid (for hindered phenols) [17], hydrochloric acid (for amino acids) [18], potassium acetate [20] and TMBS (for steroids) [19]. Silylation reactions are normally carried out under anhydrous conditions. However, it has been found, that the presence of 1 % water can substantially increase the reaction rate [9, 73]. The catalytic activity of water can be explained by the hydrolysis products of BSA [9].

For pesticide residue analysis, BSA is used as silylating agent after extraction and drying of corn grain and subsequent multi dimensional chromatography [66]. Derivatising agents for polar solutes in supercritical fluid (CO_2, N_2O) have been studied. Octadecane-carboxylic acids, -alcohols, -amines,-phosphite and –thiol can be silylated with BSA [67] (for the effeciency of the different catalysts in the silylation of ketosteroids, compare also with reference [21]). The mass spectrometric identification of 2-hydroxydodecanedioic acid and its homologues has been described [74]. A new catalyst is silica 600 ppm [65].The catalyst system is used to react silica gel with BSA under conditions useful for end-capping HPLC bonded phase packings.

A mixture of BSA/TMSIM/TMCS (1:1:1 [2, 22] or 3:3:2 [2, 9, 15, 37] is one of the most potent general silylating agents.
The 3:3:2 mixture is available from Fluka (85433, 85436).

BSA has been shown to be the reagent of choice for the simultaneous silylation of amino and hydroxyl groups [23, 70], for the detection of diethanolamines and their degradation products [24], for the simultaneous determination of metoprolol and its metabolites [25], for carbohydrates [26] and for silicate anions [32, 33]. Comparative data with other silylating agents are given for amino acids [27], hindered phenols [17], carbohydrates [13], nucleosides and their constituents [12, 28], steroids [9, 11], prostaglandins [29], trichothecenes [15], vapor phase silylations of alcohols [30] and miscellaneous compounds [31].

Some applications of BSA are cited for the silylation of nucleosides [34], 2,4-dodecadienoic acids [35], iminodicarboxylic acids [36], steroids [37] especially for GC-MS for steroid analysis [64], acidic metabolites [38], trichothecenes [15, 39], monoterpene alcohols [40], cortisols [76], aloenin (in cosmetics) [77] and carbohydrates [26].

Synthetic applications

In spite of its merits (high silylation potential, neutral silylating conditions, relatively low price), BSA is not so commonly used as silylating agent in preparative organic chemistry. J. F. Klebe et al. [8] were the first to describe the silylation of amides, ureas, amino acids, hindered phenols, carboxylic acids and enols with BSA. Later, BSA was used for the silylation of hindered hydroxyl groups [41, 42], 1,2-diols [43], 1-monoglycerides [44], phenolic hydroxyl groups [45], carboxylic acids [46, 47, 48, 75], amino acids [49, 71], squaric acids [50, 51], secondary amides [52, 53], hydrazines [54], nitro compounds [55, 56] (yielding TMS-nitronates), α- and β-ketoesters [57, 58], 4,6-dihydroxy-2-pyrone [59], sulfoximines [60] and in nucleoside synthesis [61]. N^6-benzoyladenine [68] and mono phosphoric acid esters [69] are silylated with

BSA. Y. Tanabe et al. described the silylation of alcoholic groups with BSA and TBAF as catalyst in THF or dichloromethane as solvent [78] in quantitative yields. Under these conditions, primary amines were unaffected.

J. Dedier at al. [62] described the regio- and stereoselective preparation of silyl enol ethers from different carbonyl compounds with BSA in HMPA in the presence of very small quantities of sodium metal. If 1,1-dihydroxy-compounds were silylated with BSA, acetamido derivatives resulted [63]. Michael reactions of α-isocyanoesters with α,β-unsaturated ketones work well in the presence of BSA [72].

Typical preparative procedure
Preparation of N-TMS-p-nitroacetanilide [8]: Place a mixture of 18.0 g of p-nitroacetanilide, 25.0 g of BSA, and about 30 ml of acetonitrile in a flask fitted with reflux condenser and heat on a steam bath; a "Drierite" tube prevents contact with air moisture. A clear solution is obtained after 5 min. Remove the solvent and $CH_3CONHSiMe_3$ in vacuo; the monosilylamide sublimes rapidly at 0.2 mbar at 50°C bath temperature. Distill the dark yellow residue in a small distillation apparatus without separation column, bp 88–90°C (0.3 mbar). Very litte forerun and residue are obtained. The yellow distillate solidifies on cooling and can be recrystallised from dry hexane, mp. 64–67°C.

Procedure for compounds which can only be silylated with difficulty, for GC:
1. Combine 5–10 mg sample (not recommended for sugars), 500 µl BSA and 1.0 ml solvent (acetonitrile recommended for amino acids) in a 3.0 ml Reacti-Vial™ miniature reaction vial.
2. Shake for 30 seconds. Heat at 70°C for 15 min to facilitate silylation.
3. Analyse by gas chromatography

For silylating amino acids, it is recommended that about 3 parts of solvent, preferably acetonitrile, be used to each part of BSA.

Procedure for the silylation of hydroxyl groups in sterically unhindered positions in steroids (3, 7, 16, 17[sec], 20, and 21 positions in the steroid structure) in sample preparation for GC:
1. Combine 0.1–5.0 mg of sample, 0.2–0.4 ml BSA, 0.1–0.2 ml pyridine in a 1 ml Reacti-Vial™ miniature reaction vial. If material is not soluble in BSA, add 0.1–0.2 ml pyridine.
2. Cap the Reacti-Vial™ miniature reaction vial and shake well to dissolve; reaction may be warmed to 60°C to ease dissolution.
3. Analyse by gas chromatography.

Material is silylated at room temperature within times varying from a few minutes to a few hours. Heating will hasten reaction.

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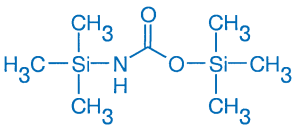

3.1.3 N,O-Bis(trimethylsilyl)carbamate, BSC

BSC, a useful silylating reagent, was developed by L. Birkofer and P. Sommer [1]. It has been described as an excellent reagent for the silylation of alcohols, phenols and carboxylic acids. The particular advantage of BSC over other silylation reagents is that the only by-products of silylation are the gases NH_3 and CO_2. Amino groups are not silylated, but trimethylsiloxycarbonylated by BSC [2, 3].

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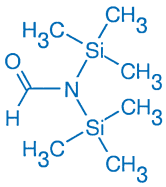

3.1.4 N,N-Bis(trimethylsilyl)formamide, BSF

The reaction of N,N-bis(trimethylsilyl)formamide with enolisable CH_2-active carbonyl compounds gives O-silylated products and N-(trimethylsilyl)formamide (for example trimethylsilylenolethers from ketones). Reaction of BSF with non enolisable CH_2-active compounds affords aminomethylene compounds and hexamethylsiloxane [1]. Ketones condense with BSF to 1-formamido-1-(trimethylsiloxy)alkanes [5].

On reacting N,N-bis(trimethylsilyl)formamide with acid chlorides, N-formyl-carboxamide and trimethylchlorosilane were formed. Isocyanates react with N,N-bis(trimethylsilyl)formamide to yield 1,3 disubstituted 1,3,5-triazine-2,4-1H-3H-dione. Amide acetals give N-formylformamidines [2]. Preparation of NTMS-imines or N-TMS-aldimines is possible starting from organolithiums [3, 4] for the preparation of β-lactams [4].

Typical procedure:
Synthesis of ethyl-3-(trimethylsilyloxy)crotonate [1]:
Treat 10.4 g (0.08 mol) ethylacetate at room temperature with 7.6 g (0.04 mol) N,N-bis-(trimethylsilyl)formamide. Stir the mixture at 70°C for 1h and after cooling to room temperature, separate the upper layer and fractionate. Yield: 67 %, bp 82–84°C / 17 mbar.

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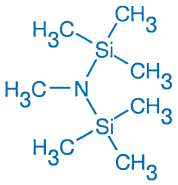

3.1.5 N,N-Bis(trimethylsilyl)methylamine

N,N-Bis(trimethylsilyl)methylamine has about the same silylation potential as HMDS and can be used in the same manner [1]. Its reaction by-product is the gaseous methylamine.

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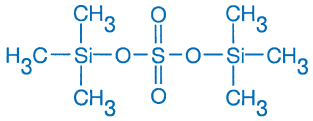

3.1.6 Bis(trimethylsilyl) sulfate, BSS

BSS, first prepared by L. H. Sommer and coworkers [1], can be used as Lewis acid [2, 3, 4, 5], as sulfuration reagent [6, 7] and as silylating agent. Active hydrogen compounds such as hydrochloric acid and ammonia [1] as well as various salts of organic and inorganic acids [6, 8] can be silylated by BSS. A mixture of HMDS and BSS has been described in a patent [9] as a useful silylating agent – better than HMDS/TMCS or HMDS/$(NH_4)_2$ SO_4 – for alcohols, hindered phenols, carboxylic acids and secondary amines. G. Simchen showed BSS to be a highly reactive silylating agent for enolisable ketones and compared it with nine other silylating agents [10]. Under mild reaction conditions only one TMS group of BSS is transferred in most cases.

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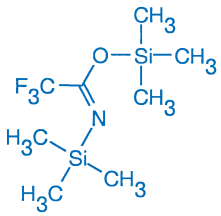

3.1.7 N,O-Bis(trimethylsilyl)trifluoroacetamide, BSTFA

BSTFA, introduced by D. L. Stalling et al. [1], is the most commonly used trimethylsilylating agent today for the analytical derivatisation of a large number of X-H acidic compounds [2, 3, 4, 5]. Its silylating potential is similar to that of BSA and MSTFA [50], depending on the substrates and conditions.

Analytic applications

BSTFA has two main advantages over BSA in gas chromatography: BSTFA and its by-products mono(trimethylsilyl)trifluorocetamide and trifluoracetamide are more volatile than BSA or its by products and so cause less interference in chromatograms; and the presence of fluorine atoms results in less fouling of flame-ionisation detectors by deposits of silica.

Because of its polar nature, BSTFA – like BSA – is able to act as its own solvent. The best results are obtained when the reaction products are soluble in the reaction medium. When problems of solubility are encountered the use of a solvent should be considered, although the dissolution of analytes prior to silylation is not always essential, as this can occur as derivatisation proceeds. The use of solvents of different polarity influences the TMS donor strength [6, 7, 8, 9]. The silylating power of BSTFA can also be increased by the addition of a catalyst, mainly TMCS (1–50 %) [9–19]. A silylating mixture of BSTFA with 1% TMCS is available from Fluka for silylation of derivatives (19918, see also the section on silylating mixtures). The influence of different solvents and other silylating reagents was studied by C. W. Gehrke and A. B. Patel [7].

Catalysts such as trifluoracetic acid [20, 21], HCl [8], potassium acetate [38, 39], O-methylhydroxylamine hydrochloride [41], piperidine [22, 49], or pyridine [9, 21] (which is often used as a solvent [6, 7, 14] as well) can also be used. Mixtures with TMSIM and TMCS (3:2:2) [19, 23] or with TMSDEA and TMCS [12] are strong and sometimes useful silylating agents for complex molecules. BSTFA in a mixture with TMSIM and TMCS (3:3:2) is also available from Fluka (85433, 85436).

References for a variety of applications in GC and MS are given in the literature [2, 3, 4, 5]. Some important references are cited here for the silylation of the following classes of substances:
amino acids [11, 12], steroids [11, 13, 40], steryl ferulates [60], 11-dehydro-thromboxane [61], 6-ketoprostaglandin $F_{1\alpha}$ [63]. Isolated metabolites and reference compounds can be silylated with a mixture of BSA/TMCS (8:2) and identified by GC-MS as trimethylsilyl derivatives [53]. The conversion of steroids for gasphase analytical studies has been described by E. M. Chambez and E. C. Horning. Different silylating reagents for structure analysis of steroids were used in [13], in which the optimal reaction conditions were shown to transform hydroxyl groups into trimethylsilylethers, and the oxo-group in the α-position to a hydroxyl group was transformed to the endiol trimethylsilyl ether. Steroids with free oxo groups react under strong conditions to form the enol trimethylsilyl derivatives. [40] describes the silylation of catecholestrogen for GC-MS analysis. Trimethylsilyl ribonucleoside derivatives have been prepared from nucleic acids and their constitutents by silylation with BSTFA [7, 9, 24, 25]. In [25] BSTFA is described as the best

silylating agent for ribonucleosides for gas chromatography. 1,6-Dimethyladenosine from human cancer urine was silylated with BSTFA [54]. Carbohydrates, such as desulfoglucosinolates [16, 14] were silylated by B. W. Christensen, and sugars by F. M. Rubino [62].

Silylating with a mixture of BSTFA/TMCS has been reported by H. Pang [24]. A number of trichothecenes were silylated for GC analysis with BSTFA and BSTFA/TMCS (4:1) [19]. Tetrahydrocannabinols and metabolites [15], prostaglandins [22], acidic metabolites [26], dicarboxylic acids [42], phenolic acids (with BSTFA, containing 1% of TMCS) [43], hydroxy fatty acid esters [44], α-keto acids [27, 28], iminodicarboxylic acids [8, 29], imino derivatives of alanine [45], alcohols [46, 47] (for GC-IR [47]), dilute hydroxy compounds in aqueous solution [17, 18] and carbonyl compounds [48] have been silylated with BSTFA. 11-Pentafluorobenzylester derivatives of 11-dehydrothromboxane B_2 and B_3 [58] and β-agonistic drugs in urine of meat producing animals can likewise be derivatised [51].

Different carboxylic acids have been chromatographed by flash-heater silylation [30], β-blocking agents [31] and aliphatic diols [32] by on-column silylation. If DMF is used as a solvent for the silylation of secondary amines, N-(aminomethylene)-2,2,2-trifluoracetamides can be formed instead of the TMS-derivatives [33]. N-Trifluoroacetyl (TFA) amino acids give the bis(TMS)derivatives, N,O-bis-TFA-serine and threonine the silylated azlactones [34]. Comparative data with other silylating agents are given in the references [7, 9, 10, 12, 13, 14, 19].

Synthetic applications
BSTFA is seldom used in synthetic organic chemistry, probably because it is more expensive than BSA. It has been employed for the silylation of nitro-compounds [35], 5,6-dibromo (or 5,6-epoxy) 1-phenyl-3,8-phosphonanedione-1-oxide [36] and of 1α,2β-epoxy-17β-hydroxy-5α-estran-3-one [37]. Protection of secondary alcohol groups in DMF has been described [55], likewise the O-silylation of acylcobalt tetracarbonyls with BSTFA [56]. Michael analogous reactions with α, β unsaturated ketones and α-isocyano-carboxylic acid esters and BSTFA by means of fluoride catalysis were studied by M. Murakami et al. [57].

Typical procedures
Silylation of amino acids for chromatography [11]:
The trimethylsilylating reaction is conducted in a closed tube, heated in an oil bath. The derivatisation conditions are 0.5 ml of BSTFA/acetonitrile (1:1, v/v) for each 1 mg of total amino acids and heating for 2.5 h at 150°C. The use of 1% TMCS has a catalytic effect on silylation of steroids [10].

Procedure for compounds which can only be silylated with difficulty, for GC:
1. Combine 5–10 mg sample (not recommended for sugars), 500 µl BSA or BSTFA or MSTFA and 1.0 ml solvent (acetonitrile recommended for amino acids) in a 3.0 ml Reacti-Vial™ miniature reaction vial.
2. Shake for 30 seconds. Heat at 70°C for 15 min to facilitate silylation.
3. Analyse by gas chromatography.

Note: it is recommended that about 3 parts of solvent, preferably acetonitrile, be used to each part of BSA for silylating amino acids.

Preparation of trimethylsilyl ethers of methylboronates of alcohols [59]:
Add methylboronic acid (1 molar proportion) in dry pyridine to the steroid diol (100 µg) and keep the mixture at 60°C for 30 min. The silylation is carried out after removal of the solvent by treating the methylboronate with BSTFA (5 µl) and heating at 60°C for 2 min or with BSTFA in DMF (20 µl, 1:3 v/v) at 60°C for 5 min. Evaporate the solution to dryness and dissolve the residue in ethyl acetate for GC and GC-MS analysis.

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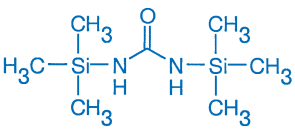

3.1.8 N,N'-Bis(trimethylsilyl)urea, BSU

BSU is a useful silylating agent with several advantages: high silylating potential, neutral reaction conditions (no catalyst necessary) and low price [1]

First mentioned as silylating agent in industrial applications (in the production of semi-synthetic penicillins and cephalosporins [2, 3, 4]), BSU has been shown by W. Verboom et al., to be a useful silylating agent for alcohols and carboxylic acids [1]. Silylations are carried out normally in dichloromethane, the by-product urea can be removed by filtration [1]. The silylation of alcohols was carried out with catalytic amounts of TBAF in dichloromethane or DMF. Carboxylic acid functions are unaffected [6]. Primary amines are silylated in situ with dimethylsulfoxide as solvent [5].

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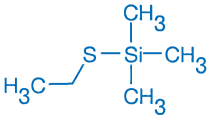

3.1.9 (Ethylthio)trimethylsilane

(Ethylthio)trimethylsilane, a useful reagent for the preparation of dithio acetals [1, 2, 3], trithioorthoesters [4], S-ethyl thioesters [5] and ethylalkylsulfides [6], can also react as a silylating agent. E. W. Abel [7, 8] has described the silylation reactions of alcohols, thiols, amines and carboxylic acids. Phosphoric acid monoalkyl esters can be silylated by (ethylthio)trimethylsilane yielding bis(trimethylsilyl)-alkylphosphites [9].

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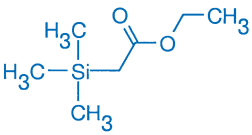

3.1.10 Ethyl trimethylsilylacetate, ETSA

E. Nakamura [1, 2, 3] and A. Gambacorta [6] described the silylation of ketones, alcohols, acetylenes and thiols with ETSA and a catalytic amount of tetrabutylammonium fluoride. The mild and operationally simple silylation procedure works under nearly neutral conditions. Another advantage is the volatility of the only by-product ethyl acetate. Ketones are silylated stereo- and regioselectively by ETSA/TBAF [3, 4, 5, 6] whereas epoxides, esters and nitriles do not react. Alkyl halides and aldehydes are incompatible with this silylation method [3].

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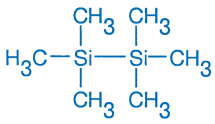

3.1.11 Hexamethyldisilane

Hexamethyldisilane is a versatile reagent in organic synthesis e. g. for the generation of trimethylsilyl anions [1–3]. It can also be used for the silylation of enolisable ketones in HMPA together with catalytic amounts of sodium [4]. The synthesis of 4-trimethylsilyl-1-nitrobenzene [5], N,O-bissilylated hydroxylamines from hydroxylamine hydrochloride [6], polysilylated hydrazines [7] and the silylation of vinyl-halides [8] have been reported. The addition to a C-C triple bond is described by Y. Ito and co-workers [9]. 1-Iodo-1-trimethylsilyl-alkenes are prepared by silylation of aldehydes with hexamethyldisilane and tetrabutylammoniumfluoride as catalyst in HMPA and then treatment with $(PhO)_3$ PMeI [10]. Y. Tanabe and co-workers have described the silylation of citronellol, linalool and terpinen-4-ol (alcohol silylation) with a catalytic amount of TBAF [11].

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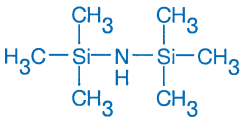

3.1.12 Hexamethyldisilazane, HMDS

HMDS is one of the original reagents used to prepare TMS derivatives. Its first application as silylating agent was described in the early 1950s [1]. Although, it is not a strong TMS donor when compared with subsequently introduced reagents, nevertheless it continues to be employed because of many advantages:

- it is inexpensive
- it has a relatively low boiling point (124 – 127° C)
- the only reaction by-product NH_3 can leave the reaction mixture driving the reaction to completion

– it reacts more selectively than stronger silylating agents
– its silylating power can be increased by different (mostly acidic) catalysts
– it can be used without solvent

Although HMDS is normally used in excess, both silylating groups are available for the silylation. Most functional groups can be silylated by HMDS and, depending on the substrates, the addition of a catalyst or/and application of heat may be necessary.

HMDS alone is normally a very poor silylating agent, but acidic substrates, which act as their own catalysts, are readily silylated. The procedure works generally by heating the mixture under reflux until no more NH_3 is evoled. To illustrate, the silylation of a O,O-diethyl-N-formylphosphoramidate with HMDS was carried out in benzene by refluxing [87]. Thus, the silylated product reacts with NH_3 to form a Nphosphorylated formamidine. To increase the silylating potential of HMDS the following catalysts are commonly used: TMCS [1–3], $(NH_4)_2SO_4$ [1, 4], H_2SO_4 [5–7] and imidazole [8, 9]. More seldom used are TMBS [10, 11], TMIS [12–14, 88], TMCS/LiI [15], BSS [16], TFA [17–19] and sulfonic acids [20]. Another group of catalysts (e.g. saccharine) has been described [21]. Mixtures of TMCS and HMDS [1, 22] are common silylating agents and are available from Fluka as ready-to-use reagents. For more details see the section on "silylating mixtures".

Analytical applications
The use of HMDS for analytical purposes has been comprehensively reviewed by A. E. Pierce [1]. Applications are compiled in the references [24–27, 89].

HMDS alone is usually applied only for the silylation of acidic substrates (e.g. carboxylic acids and amino acids [3], N-TFA-amino acids [28]). Nevertheless non-hindered alcohols and phenols can be silylated by HMDS alone [1, 24–27]. An appropriate solvent (pyridine, DMF, DMSO) may increase the reaction rate. Hydroxylated steroids are partially silylated by HMDS without catalyst (only the unhindered hydroxyl groups react) [29]. This procedure has been used for GC-separations [30].

Normally, HMDS is used with a catalyst, mostly TMCS (see the section on silylating mixtures). The fine precipitate of NH_4Cl which is often produced during derivatisation does not affect the chromatography. TMBS has been described by L. Aringer and coworkers to be a stronger catalyst than TMCS in the silylation of steroids [10, 11]. O-Methylhydroxylamine hydrochloride shows catalytic activity in the silylation of the hindered hydroxyl group of the steroid methanedienone by HMDS [31]. $(NH_4)_2SO_4$ is also a powerful catalyst [1] but only seldom used in newer applications.

Trifluoroacetic acid is a very effective catalyst as shown for the silylation of organic acids [97], carbohydrates [17, 19, 97], hindered phenols [18], disaccharides [19] and monosaccharide oximes [38]. Amino acids give almost quantitatively N-trifluoroacetyl-amino acid trimethylsilylesters by simultaneous reaction with trifluoroacetic acid and HMDS [39].

HMDS was used for the determination of fluoride as trimethylfluorosilane [40].

HMDS is also important for the silylation of inorganic material such as glass [41], silica gel [42, 43] and particularly glass capillary columns [44, 45].

Synthetic applications
Because of the advantages mentioned, HMDS is very frequently used in preparative organic chemistry. Basic substrates such as amines were silylated only very sluggishly without a catalyst [2, 3]. The in situ monosilylation of primary amines without isolation was described [92]. Addition of an acidic catalyst leads to the formation of silylated amines in low to good yields. The following catalysts have been used (typical substrate and yield in parentheses):
– TMCS (n-pentylamine, monosilylation, 51 % yield [2]; n-octylamine, monosilylation, 56 % yield [3]; pyrrolidine, 62 % [20],
– $(NH_4)_2SO_4$ (n-butylamine, disilylation, 30 % [46], piperidine, 55 % [4]; allylamine, mono- [47], disilylation [48]),
– H_2SO_4 (imidazole, 85 % [5]; tetrahydropyrimidines [49]),
– HCl (dopamine, O,O',N-trisilylation, 89 % [50],
– saccharine (p-toluidine, monosilylation, 83 % [21]),
– TMCS/LiI (o-toluidine, monosilylation 92 % [15]),
– bis(trimethylsilyl)sulfate (ethylene diamine, aniline [16]).

An evaluation of catalysts for the silylation of piperidine was given in ref. [4].

Normally, thiols were silylated by HMDS only in the presence of a catalyst: good yields were achieved with imidazole [9, 51], saccharine [21] and bis(4-nitrophenyl)-N-(tosyl)phosphoramidate [21], whereas TMCS was less satisfactory [2]. L-Cysteine as its hydrochloride forms the O,S,N-trisilylated product in 73 % yield [52]. Thiophenols can also be silylated without a catalyst [53, 64].

Alcohols [2, 3, 54], especially those with electron withdrawing groups in the α-, β- or γ- position [55, 56, 93, 94] can be silylated by HMDS without any catalyst. Nevertheless the catalysed procedures give better yields in a shorter time at lower temperatures. The most frequently used catalysts are TMCS [2, 3, 57], $(NH_4)_2SO_4$ [54, 58], H_2SO_4 [7] and imidazole [9]. (Bistrimethylsilyl) sulfate (BSS) [16] has been described in a patent to be a more efficient catalyst for the silylation of

hindered phenols than TMCS and $(NH_4)_2SO_4$. Four powerful catalysts (e.g. saccharine) have been proposed [21]. Likewise, mixtures of HMDS with an electrophilic silylating agent such as BSS [16], TMCS [14, 22, 59, 60] and trimethyliodosilane [14] are very efficient. A very useful and widely employed mixture (particularly for analytic derivatisation) consisting of HMDS/TMCS with pyridine as solvent, has been described in the classical paper of C. C. Sweeley at al. [22] for the silylation of carbohydrates. For more information about silylation with a mixture of HMDS/TMCS see also the section on "silylating mixtures".

Enols (1,3-dicarbonyl compounds [8, 61, 62], 1,3-enaminones [63]) are conveniently O-silylated by HMDS alone [61–63] or catalysed by imidazole [8]. A mixture of HMDS/trimethyliodosilane (molar ratio 1,1:1) converts ketones efficiently to the thermodynamically equilibrated silyl enol ethers [12, 13] (for more details and references see under trimethyliodosilane).

HMDS (mainly catalysed by $(NH_4)_2\ SO_4$) is widely used for the silylation of nucleic acid bases and related compounds [65–68, 83, 86], as well as in silylation-amination reactions [20]. H. Vorbrüggen and B. Bennua described a one-step nucleoside synthesis with HMDS/TMCS and a catalyst (e.g. perfluorobutanesulfonic acid) [69].

Acidic compounds such as carboxylic acids are rapidly silylated by HMDS without a catalyst [3, 70, 71]. Heterocyclic trimethylsilyl carboxylates can be prepared simply and in very good yields from heterocyclic carboxylic acids and HMDS [95]. Nevertheless the presence of a catalyst leads to shorter reaction times and lower reaction temperatures. The following catalysts have been used: TMCS [3], $(NH_4)_2SO_4$ [72], saccharine [21], bis(4-nitrophenyl)-N-(tosyl) phosphoramidate [21], tetraphenyliminodiphosphate [21] and BSS [16]. Amino acids have been silylated with catalysts, such as HCl [52], H_2SO_4 [5, 6], $(NH_4)_2\ SO_4$ [72], TMCS [3, 73], saccharine [21, 74] and p-toluenesulfonic acid [85].

Some examples of further classes of substances which have been silylated by HMDS with or without catalyst are as follows: carboxylic acid amides [7, 21, 74, 75], urea [21], sulfonamides [76, 86], sulfamide [76, 86], phosphoramidates [77, 78], phosphonoamidates [78], hydroxamic acids [79, 80], N-substituted hydroxylamines [21, 81, 82] and alkylphosphites [21, 84]. Thiolactams were silylated at the nitrogen atom [90] and 3,4 substituted lactams were N-alkylated via the silylation of nitrogen [91]. The bis-silylation of a C-C triple bond is described in [96].

Typical procedures
Silylation of an alcohol with HMDS [2]:
Add 17.6 g (0.11 mol) of HMDS to 12.0 g (0.2 mol) of propyl alcohol in a flask equipped with condenser and drying tube. The reaction temperature is raised to 93°C over a period of 5 hr., with accompanying refluxing and evolution of ammonia. The 26.5 g of distillable crude product with b.p. 88–103°C is an azeotrope of TMS ether/alcohol.

Silylation of sugars and related substances for GC:
1. Place 60–70 mg of 80 % solids syrup in a Reacti-Vial™ miniature reaction vial.
2. Dissolve in 1 ml pyridine.
3. Add 0.9 ml HMDS and mix.
4. Add 0.1 ml trifluoroacetic acid.
5. Shake vigorously for 30 sec.
6. Allow to stand for 15 min.
7. Analyse by gas chromatography.

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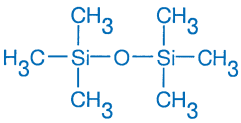

3.1.13 Hexamethyldisiloxane, HMDSO

HMDSO is a very poor silylating agent. It is the end product of the hydrolysis of every trimethylsilylating agent. Nevertheless M. G. Voronkov [1] demonstrated in 1959 that alcohols and phenols can be silylated by HMDSO. The reaction is catalysed and formed water is eliminated by azeotropic distillation. This method was again described for the silylation of alcohols and phenols [2] (catalysts: p-toluenesulfonic acid or pyridinium p-toluenesulfonate) and further extended to carboxylic acids [3] (catalyst: sulfuric acid).

TMS esters of most inorganic acids [4] (e. g. sulfuric acid [5, 6], hydroiodic acid [7], polyphosphoric acid [8, 9] and trifluoromethanesulfonic acid [10]) can be prepared from HMDSO and an appropriate acid derivative.

HMDSO alone or as a mixture with TMCS is often used in inorganic analytical chemistry e. g. for the silylation of various kinds of silicates [11–17] (in minerals, cements, pastes, soil etc.), boric acid [18] and fluorides [19, 20]

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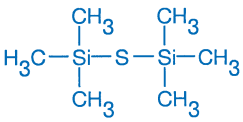

3.1.14 Hexamethyldisilthiane

Hexamethyldisilthiane, a useful synthetic reagent e.g. for the transfer of sulfur to carbon [1, 2, 3], the preparation of thioanhydrides [4, 5], sulfides [6], allylsulfides from allyl alcohols and thiols [14], THF soluble Li_2S [7] and the reduction of sulfoxides [8, 9], is also a powerful silylating agent. E. W. Abel [10] has described the silylation of alcohols, thiols, amines and carboxylic acids. Organometallic acids have been silylated likewise [11]. A. Ricci and co-workers [12] have shown that hexamethyldisilthiane can be used for the silylation of 1-methylpyrrol-2(5H)-one and thiophen-2(5H)-one. By reaction of hexamethyldisilthiane with S-propylmethylphosphonochloridothionate, S-propyl-O-(trimethylsilyl)-methylphosphonodithionate can be formed [13]. The synthesis of β-trimethylsilylthio silyl enol ethers of acylsilanes via the Michael addition of hexamethyldisilthiane as nucleophile has been described by A. Ricci and co-workers [15].

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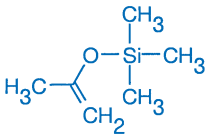

3.1.15 (Isopropenyloxy)trimethylsilane, IPOTMS

IPOTMS – first mentioned as silylating agent by M. Donike and L. Jaenicke [1] – is useful for the silylation of carboxylic acids, alcohols and phenols. An acidic catalyst (TMCS or acetic acid) is required for the silylation of alcohols and phenols. Carboxylic acids need no catalyst. The particular advantages of IPOTMS are that the reagent itself and its reaction product (acetone) are neutral and highly volatile (IPOTMS contains ~30 % hexamethyldisiloxane which is also highly volatile (bp ~100° C) and does not interfere in the silylation reaction).

IPOTMS cannot be used with amines and compounds containing certain vicinal functional groups such as α-hydroxylamines, 1,2-diols and β-mercaptoalcohols which yield heterogeneous products [1, 2, 3].

IPOTMS was used as building block in the synthesis of 1,2-oxazine from oxime [4], of ketones from alcohols and IPOTMP ($SnCl_4$ as catalyst, in CH_2Cl_2) [5], of N-methoxycarbonyl γ-oxo-α-amino acid methyl esters through Lewis acid induced coupling of chloroglycine with silyl enol ether [6]

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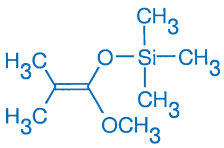

3.1.16 1-Methoxy-2-methyl-1-trimethylsiloxypropene

Y. Tamura and co-workers [1, 2] have proposed a series of ketene O-alkyl-O-silyl acetals as useful and effective silylating agents for alcohols, carboxylic acids, mercaptans, amides and ketones. The silylation [1] (exception: ketones) takes place in acetonitrile or dichloromethane and requires neither acid nor base or another catalyst. The reaction by-product, the corresponding methyl carboxylate, can be easily removed by evaporation and the pure products are rapidly isolated in almost quantitative yields. Ketones [2] are silylated in THF using tetrabutylammonium fluoride as catalyst and give the corresponding silyl enol ethers in good yields. This silylation method has also been described to be the best for the preparation of multifunctional alkylthiotrimethylsilanes [3].

1-Methoxy-2-methyl-1-trimethylsiloxypropene has not been used as trimethylsilylating agent until now, although it would be advantegeous that the sole silylating by-product was methyl isobutyrate (bp 91–93° C). E. Yoshii and K. Takeda [4] have shown that the corresponding triethylsilylderivative (1-methoxy-2-methyl-1-triethylsiloxypropene) is a useful triethylsilylating agent for hydroxyl groups: primary

alcohols need no catalyst, the silylation of tertiary alcohols can be promoted by the addition of a trace amount of trifluoromethanesulfonic acid.

1-Methoxy-2-methyl-1-trimethylsiloxypropene has been used as coupling reagent with lactones [5] and aldehydes, ketones, carboxylic acid esters (aldol additions) [6, 7, 8]. Coupling reactions of benzylic and allylic sulfides with O-silylated enolates have been described [9].

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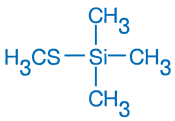

3.1.17 (Methylthio)trimethylsilane

(Methylthio)trimethylsilane, a useful reagent for thioacetalisation [1], can also react as silylating agent. E. W. Abel [2, 3] has described the silylating properties of different (alkylthio)trimethylsilanes, and A. Ricci and co-workers [4] have shown that (methylthio)trimethylsilane can silylate 1-methylpyrrol-2(5H)-one and thiophen-2(5H)-one. (Methylthio)trimethylsilane reacts with propenoyltrimethylsilanes to form a functionalised silyl enol ether of acylsilanes in good yield [5].

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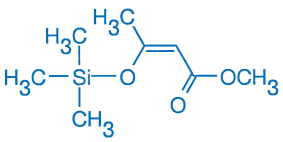

3.1.18 Methyl 3-trimethylsiloxy-2-butenoate

The trimethylsilyl enol ether of methyl acetoacetate was shown by T. Veysoglu and L. A. Mitscher [1] to be a very potent silylating agent. Primary, secondary and even tertiary alcohols are silylated quantitatively in a few minutes at room temperature without any catalytic assistance. The procedure can take place without solvent, however a polar solvent will increase the silylation potential. The only by-product of the reaction is methyl acetoacetate (bp 170°C).

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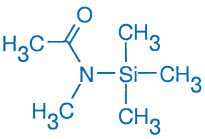

3.1.19 N-Methyl-N-trimethylsilyl-acetamide, MSA

In 1967 L. Birkofer and M. Donike [1] proposed MSA as a strong and useful silylating agent for polar substances. Its silylating potential is very high but slightly less than that of MSTFA, BSA and BSTFA [2,3,4].

Analytical applications
The advantages of MSA over other silylamides are: its high dipole moment which enables it to act as solvent for polar substances, and, compared to MSTFA, its lower price. It has been used to silylate amino acids. Normally, the silylation of amino acids and amines with trimethylsilylamines like diethyl trimethylsilylamine or HMDS is tedious and circumstantial. To achieve an analytical process with mild reaction conditions and short reaction times, N-trimethylsilylamides, like MSA can be used. The silylated amines or amino acids can be used without any other operations for GC-analysis. MSA has been used to silylate amino acids [1,5], fatty acids [1], polyalcohols [1], carbohydrates [1], amines and amine hydrochlorides [1], phenol-alkylamines [1], hypoxanthine [6] and guanine[6].

Synthetic applications
MSA has been employed for the preparative silylation of primary amines [10, 12], amino acids [7], dipeptides [8] and 6-aminopenicillanic acid [9]. 2-Bromoethylamine hydrobromide can be silylated directly with MSA yielding the N,N-bis-TMS derivative [10]. Dopamine hydrochloride gives the tetra-TMS derivative in good yield [11] with excess MSA (TMCS/Et_3N, TMSIM and HMDS give only the bis- or tris-TMS derivative, respectively).

Typical procedure
Derivatisation for chromatography [1]:
1. Treat 1–2 mg of the substance with 100 µl of MSA.
2. Shake for 5 min at room temperature.
3. If the substance has not dissolved, let warm at 60–100°C.
4. GC-analysis

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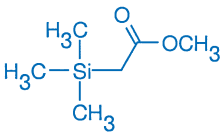

3.1.20 Methyl trimethylsilylacetate

Methyl trimethylsilylacetate in the presence of TBAF, has been used in the same way as ethyl trimethylsilylacetate (3.1.9) for the silylation of tertiary hydroxyl groups and enolisable ketones [1, 2]. It was used as reagent for coupling with carbonyls by deprotonation with LDA to generate the enolate [3–7].

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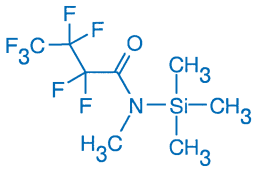

3.1.21 N-Methyl-N-trimethylsilylheptafluorobutyramide, MSHFBA

MSHFBA was developed as silylating reagent for GC purposes to produce even less fouling of the FID than with MSTFA. The silylation potential of MSHFBA has been found to be a little higher than that of MSTFA [3] and can be increased by addition of catalytical amounts of TMCS [1, 2].

MSHFBA has been used for the silylation of phenolic compounds [1, 2], aminoalkylphenols [1, 2, 4], glucosinolates in seeds and leaves [5], carbohydrates (catalysed by TMCS) [6] and hydroxysteroids [7]. If MSHFBA is employed as the acylation reagent in the selective simultaneous N-perfluoroacylation-O-trimethylsilylation of aminoalkyl-phenols, hydroxy amines and amino acids, the use of MSHFBA is advantageous in the silylation step. During this silylation it is neccesary to control the silylation potential of MSHFBA by addition of heptafluorobutyric acid and a colour indicator [4].

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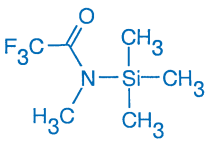

3.1.22 N-Methyl-N-trimethylsilyltrifluoroacetamide, MSTFA

MSTFA, introduced by M. Donike [1], has similar reaction properties to BSA and BSTFA as TMS donor and can be used for the silylation of all protic functional groups. Its particular advantage over BSA, MSA and BSTFA is that the reagent itself and its by-product, N-methyltrifluoroacetamide, are even more volatile than BSTFA and its by-products [1].

Analytical applications

MSTFA has become one of the most important silylating agents for analytical purposes. It can be used without solvent. Due to its polarity it can dissolve even highly polar substances such as amino acid hydrochlorides [1]. However M. Donike [2] showed that addition of trifluoroacetic acid as co-solvent is very useful for the silylation of polar compounds. Other frequently used solvents are acetonitrile and pyridine.

The silylation potential of MSTFA is similar to that of BSA and BSTFA [3]. It can be increased by addition of a catalyst – mainly TMCS [1, 4, 5]. Other catalysts are TMSIM (for the silylation of indolyl-NH) [7, 8], potassium acetate [5, 6], TMBS and TMIS [6] (for the quantitative derivatisation of ketosteroids as their silyl enol ethers).

MSTFA has been used for the silylation of various polar compounds [1, 2, 4, 9]. Trimethylsilylether derivatives of anabolic steroids in bovine urine, which contain only hydroxyl functional groups (e. g. stilbenes, estradiol-like compounds) can be synthesised for gas chromatography-mass spectrometry analysis [30]. Carboxylic acids such as fatty acids (capric acid C_{10}, myristic acid C_{14}, stearic acid C_{18}, behemic acid C_{22}, hexacosanic acid C_{26}, mellisic acid C_{30}), can likewise be silylated in a mixture of pyridine / hexane = 1:1 [11] or in n-hexane [10]. The N-nitroso compounds of sarcosine, proline and 2-hydroxyproline were synthesised and silylated [12].

The silylation of β-ketoesters to the 3-trimethylsiloxy-2-alkene acid-alkylester has been described for four acidic esters (3-oxobutanoic acid trimethylsilylester, 3-oxooctanoic acid trimethylsilylester, 3-oxotetradecanoic acid trimethylsilylester and 3-oxodecanedioic

acid bis(trimethylsilyl)ester [13]. Ureas and anilines, e.g. 4-chloroaniline, 3.4-dichloroaniline and 4-chloro-3-trifluoromethylaniline as degradation standards of antimicrobial agents have been studied via silylation with BSTFA [14].

Nucleic acids and their constituents [15], hindered phenols (with a mixture of MSTFA and 1% TMCS in pyridine as solvent) [16], 2- and 4- TMS-hydroxyacetophenones [31] and metabolites of piperidine in urine [17] have been silylated. Aminoalkyl-phenols can be derivatised to N-trifluoracetyl-O-TMS-aminoalkyl-phenols simultaneously by MSTFA and N-methyl-bis-(trifluoracetamide) (MBTFA) [18, 19]. During this derivatisation reaction it is neccesary to control the silylating potential of the mixture by means of a colour indicator such as methyl orange [20].

The silylating potential can be reduced by addition of trifluoroacetic acid [19, 20] or other protic substances [19]. A similar procedure was also used by M. Donike for indolalkylamines [8]. Instead of MBTFA, it is likewise possible to use N-methyl-N-bis(heptafluorobutyramide) [21]. A. S. Christopherson described the silylation and trifluoroacetylation of phenol-alkyl-amines by flash-heater derivatisation [22]

MSTFA is widely used for the silylation of steroids, for example in their structural analyses [5], for the preparation of steroid TMS-enolethers of ketosteroids for gas chromatographic and mass spectrographic studies [6] and other steroid investigations [23–27]. The derivatisation of acetals from lipid fractions of liver after reductive work-up and chromatographical separation, was done with BSTFA as silylating agent [32]. Synthesis and use of reference substances to detect the use of anabolic steroids in man have been described [37, 38]. Also, the trimethylsilylation of metabolites of anabolic agents in greyhound racing is carried out only with BSTFA [33].

Two different mixtures have been shown to be of particular use for the determination of anabolic steroids: MSTFA/TMCS/TMSIM (100:5:2) [23–25] for the silylation of hydroxyl groups only, and MSTFA/TMIS (100:2 or 500:1, containing a small amount of 1,4-dithioerythritol to reduce formed iodine) [23, 27, 34], which yielded TMS ethers as well as TMS enol ethers quantitatively (TMIS has been shown by M. Donike [6] to be the best catalyst for this purpose). The derivatisation of heptafluorobutyrates to study the metabolism of 17β,19-nortestosterone in urine of calves after administration with a MSTFA/TMIS mixture (1000:2) has been described [35]. GC-MS analyses of buprenorphine in horse urine derivatised at the phenolic hydroxyl group was accomplished by L. Debrabandere et al. [36].

Synthetic applications
H. A. Staab and C. P. Herz used MSTFA for the silylation of naphthoquinhydrones [28].

M. Gerlach and co-workers [29] showed that dopamine hydrochloride yields the tetra-TMS derivative after silylation with MSTFA (other silylating agents yield partially silylated derivatives only)

Typical procedures
Many silylations are carried out as follows: Evaporate the solvent and dry the residue using a gentle stream of dry nitrogen. Inject MSTFA and warm the mixture to 60–90°C for 15–90 min. Dissolve in dry dichloromethane and inject the sample into the GC.

For compounds with lower reactivity towards silylation:
1. Combine 5–10 mg sample (not recommended for sugars), 500 µl BSA or BSTFA or MSTFA and 1.0 ml solvent (acetonitrile recommended for amino acids) in a 3.0 ml Reacti-Vial™.
2. Shake for 30 sec. Heat at 70°C for 15 min to facilitate silylation.
3. Analyse by gas chromatography.

Note: it is recommended that about 3 parts of solvent, preferably acetonitrile, be used to each part of BSA for silylating amino acids.

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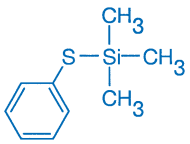

3.1.23 (Phenylthio)trimethylsilane

(Phenylthio)trimethylsilane is quite a useful reagent in organic synthesis, e.g. for the conversion of aldehydes into phenyl-alkyl-sulfides via monothioacetals [1] and for forming thioglycosides from acetals in the presence of trimethylsilyltriflate [7]. The formation of Z-1-trimethylsilyl-1,3-bis-phenylthiopropene by reaction of a vinyl silyl ketone with two equivalents of (phenylthio)trimethylsilane and $BF_3.OEt_2$ is described in [5]. 1.4-Addition to α, β-unsaturated carbonyl compounds [2] and the cleavage of methyl and benzylethers [3] is likewise a useful method in organic synthesis. By stirring (phenylthio)trimethylsilane with propenoyltrimethylsilane at room temperature, it is possible to isolate 3-phenylthio-1-trimethylsiloxy-1-trimethylsilyl propene in 98 % yield [6]. It can also be used as silylating agent in the same way as its methyl and ethyl analogues. The silylation of carboxylic acids with (phenylthio)trimethylsilane has been examined with respect to electronic and steric effects. A remarkable base catalysis has been observed [4].

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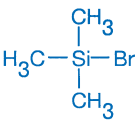

3.1.24 Trimethylbromosilane, TMBS

Trimethylbromosilane is a highly reactive silylating agent particularly useful for synthetic purposes. As with trimethyliodosilane, its chemical potential was mainly discovered in the last decade [1–4]. Its reactivity in all types of reactions is normally lower than that of trimethyliodosilane but much higher than that of trimethylchlorosilane. Its advantage over trimethyliodosilane is mainly due to its much lower sensitivity to light and oxidation. This makes working with TMBS much more convenient (trimethyliodosilane readily forms iodine which may interfere in some reactions).

Analytical applications

TMBS was hitherto only rarely applied in analytical derivatisation reactions. L. Aringer and co-workers [5, 6] described the excellent silylation properties of a reagent mixture containing HMDS, pyridine and TMBS instead of TMCS as the catalyst. They persilylate slow reacting hydroxy- and oxosteroids in gas chromatographic-mass spectrometric analysis. S. J. Gaskell et al. [7] achieved higher yelds with fewer by-products using a mixture of BSA/TMBS in pyridine. M. Donike [8] showed later on that trimethyliodosilane is a better catalyst than TMBS for the quantitative and isomerically pure formation of silyl enol ethers by silylation of hydroxyketosteroids with MSTFA.

Synthetic applications

H. H. Hergott and G. Simchen [9] showed TMBS/Et_3N to be a highly reactive silylating agent for ketones. In comparison with nine other electrophilic silylating agents, only trimethyliodosilane and TMS triflate gave higher reaction rates. Similar results on the silylating reactivity of TMBS were found later [10]. Trimethylsilyl enol ethers of α-bromocarbonyl compounds have been prepared conveniently with TMBS/Et_3N [11]. Studies of a TMBS-Ph_4SbBr system as a novel selective reagent for synthesis of silyl enol ethers from cyclic ketones are described by M. Fujiwara and co-workers [16].

K. C. Brinkman et al. [12] used TMBS for the silylation of iron carbonyl anions and iron carbene complex anions. Tetrakis-(trimethylsilyl)ated hydrazines can be formed with TMBS, when the tris(trimethylsilyl)ated hydrazine is deprotonated with BuLi [14]. Sterically overloaded pyrroles can be silylated at nitrogen, if the nitrogen-atom is deprotonated with BuLi and then the lithium-salt treated with TMBS.

Propenoyltrimethylsilane reacts with TMBS to give 3-bromo-1-trimethylsiloxy-1-(trimethylsilyl)-propene, a functionalised silyl enol ether of acylsilane [17]. The synthesis and reaction of (1-(trimethylsilyl)alkylidene)triphenylphosphorane via silylation of a phosphorus ylide has been described by H. J. Bestmann [18].

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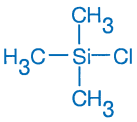

3.1.25 Trimethylchlorosilane, TMCS

TMCS is the oldest silylating agent, first used by R. O. Sauer [1] in 1944 for the silylation of alcohols. TMCS alone has a poor silylating potential, but in the presence of a base, mostly a tertiary amine, many functional groups can be silylated [2]. In analytical chemistry, TMCS is practically out of use as sole silylating agent but finds widespread application as component or catalyst in various silylating mixtures. In preparative chemistry even today TMCS is the most commonly used silylating agent and is applied in many kinds of silylations. If used as sole agent (normally by refluxing with the substrate for several hours) HCl is expelled, thus driving the reversible reaction to completion. See "typical procedures" in this chapter. In general however, it is used with a base as acid acceptor, or the substrate to be derivatised is first converted into a salt which subsequently reacts with TMCS.

Analytical applications

Earlier applications of TMCS as silylating agent (alone or with base) are compiled in ref. [2]. Nowadays TMCS is almost only used in combination with other silylating agents, either as a component in mixtures (e.g. HMDS/TMCS/pyridine, BSA/TMSIM/TMCS which are very universal and powerful silylating mixtures. Mixtures of HMDS/TMCS 2:1 (v:v), BSA/TMSIM/TMCS 3:3:2, BSTFA/TMSIM/TMCS 3:3:2 are available as ready to use silylating mixtures from Fluka (see the section on "silylating mixtures"), or as catalyst to increase their silylating potential (see the appropriate reagents for details and references on these applications.) BSA with 5 % TMCS and BSTFA with 1% TMCS are available from Fluka.

In this way, urinary metabolites of formebolone in man can be silylated with a MSTFA/TMCS/pyridine mixture for GC-MS studies [90]. Carbohydrates from carbohydrate phosphates can be silylated with a BSTFA/TMCS 9:1 mixture [91]. Fluoride has been determined by GC as TMS-flouride after silylation with TMCS [3].

TMCS was found to be less useful than silylamines for the silylation of glass (glass capillaries [4], micro electrodes [5], Aerosil 380 silica [92]). On the other hand, silylation of used glassware with 5 % TMCS in toluene has been described by L. Debrabandere [94]. Trisilanoles can be silylated with TMCS and Et_3N as base [93]. Lattice vacancy in zeolites can be identified by silylation with TMCS [95].

Synthetic applications

TMCS alone is useful for the silylation of strong acids [6] (e.g. sulfuric acid [6, 7], boric acid [6], methylphosphonic acid [6], benzenesulfonic acid [8], trifluoroacetic acid [6], nonafluorobutanoic acid [89], α-cyanoacrylic acid [96], sodium trichloroacetate in THF [97]). The components are usually heated until HCl evolution ceases. After distillation, the silylesters are obtained in good yields. Weak acids do not react well under these conditions, but if the reaction is carried out in 1,2-dichloroethane the silylation proceeds well (the reaction in 1,2-dichloroethane is about 100 times faster than in tetrachloromethane or benzene solution [9]). Alcohols and phenols can in principle be silylated with pure TMCS alone but the reaction times are long and the yields are often poor [10]. Primary amines, which react also as bases, can be silylated in diethylether with TMCS alone [101, 102].

If TMCS is used together with Li_2S in acetonitrile (neutral conditions, probably in situ formation of hexamethyldisilthiane) alcohols, phenols and secondary nitro compounds can be silylated under these mild conditions to give high yields [11]. Hexamethyldisilthiane has been prepared in high yields, starting with sulfur and Na-naphthalene in THF [98].

The preparation of tris(trimethylsilyl)amine and bis(trimethylsilyl)amine is possible. Mo and W-catalysts are used in the reaction of TMCS with Na and N_2 [116].

In most applications TMCS is used in combination with a base which acts as HCl acceptor but which influences also the reactivity of the silylating mixture [12]. Ammonia has been used by L. Birkofer [80] for the silylation of serine. Pyridine [1, 2, 10] is more frequently used e.g. for the silylation of alcohols [10, 99, 147], phenols [10, 13], carboxylic acids [14] etc. Hydrazines can be bis- and tris-trimethylsilylated with pyridine as base [100]. N-Alkylhydroxylamines are selectively O-silylated by TMCS/pyridine [15]. Substituted pyridines, such as the 2,5-dimethyl [12] and 2,4-dimethyl derivatives [12] which increase the reactivity, 2,6-dimethylpyridine [16, 85] and crosslinked poly-(4-vinylpyridine) [17] can also be employed. Ethylene glycol was bissilylated and other alcohols were silylated by addition of urea [140].

The most popular base however is triethylamine, which has been used extensively for many kinds of silylations [2]. The reactions are carried out normally in an inert apolar

solvent, and the triethylamine hydrochloride formed can be filtered off. The use of dipolar aprotic solvents increases the reactivity of TMCS/Et_3N. Some important references are given for the silylation of alcoholic hydroxyl groups [18–20], phenols [21, 22], carboxylic acid [20–23], amines [22, 24, 25, 86, 87, 101, 102], primary polyfluoro-alkylamines [109], N-methyl-hydroxylamine hydrochloride (will be bis-silylated at N and O) [105], amides [26–28], lactams [29, 30], thiolactams [103], sulfonamides [115] and nitroalkanes [31]. Pure TMCS with amino acids forms silylester hydrochlorides [32], whereas, in the presence of triethylamine as base, the amino group is monosilylated as well [32, 33, 104]. Dopamine is selectively O-silylated with stoichiometric amounts of TMCS/Et_3N, with an excess of these reagents the O,O',N-trisilylated derivative is formed [22]. H. H. Hergott and G. Simchen [34] compared the combination TMCS/Et_3N in 1,2-dichloroethane with nine other electrophilic silylating agents for the silylation of ketones and found TMCS to be the less reactive reagent. A. R. Bassindale and T. Stout [12] established similar results.

The reactivity of the system "TMCS/base" can be influenced by the nature of the base, the solvent and the catalyst. The classical method of H. O. House and co-workers [35] for the preparation of thermodynamically equilibrated TMS-enol ethers uses TMCS/Et_3N in DMF [36–42]. With $ZnCl_2$ as catalyst, an apolar solvent such as benzene can be used for this type of reaction [36–39, 43–47]. M. Schorr and W. Schmitt showed, that many primary amines can be bis-silylated with a system TMCS/Et_3N and $TiCl_4$ in catalytic amounts.

The stability of the bis-silylated amines is higher than the stability of the corresponding mono-silylated amines. As bis-silylated amines are more stable to water or alcohols under neutral or basic conditions at room temperature, the bis-(trimethylsilyl)amino moiety can be used as a protecting group in Grignard reactions [106].

LiBr [48] and NaI [49–51] have been shown to be useful catalysts for the silylation of α-bromo-ketones and various aldehydes and ketones, respectively, with TMCS/Et_3N in acetonitrile (in situ formation of TMBS and TMIS). Potassium nonaflate/TMCS/Et_3N in cyclohexane (in situ formation of TMS nonaflate) readily silylate ketones at reflux temperature [52]. G. Olah and co-workers [11] proposed the system Li_2S/TMCS/Et_3N in acetonitrile (in situ formation of hexamethyldisilthiane), as a mild and efficient silylating agent for carbonyl compounds. The silylation of a tertiary alcohol by TMCS/Et_3N in ether can be catalysed by DMSO, HMPA, DBU or imidazole [53]. Further, even more useful catalysts are N-methylimidazole and 4-dimethylaminopyridine [12] for the silylation of secondary and tertiary alcohols [112, 113], the latter also proposed by O. Hernandez [54] for silylation with TBDMSCl. Imidazole, as both catalyst and base, can be used for the silylation of alcohols in DMF [55, 56] (compare the classical method for silylation with TBDMSCl [57]).

If DBU is used as base, carbonyl compounds can be silylated efficiently in refluxing dichloromethane [88] (sometimes catalytical amounts of silver salts are helpful). The use of DBU as base for the silylation of other functional groups with TBDMSCl has also been described [58, 59]. The combination of ethyldiisopropylamine/TMCS has been used for the silylation of a δ-bromoaldehyde [60] in DMF and for the selective S-silylation of 2-aminoethanethiol hydrochloride in acetonitrile [61] (ethyldiisopropylamine has also been described as being an effective base for silylation with TBDMSCl [62]).

Phase-transfer catalysis has been applied for the silylation of various alcohols [63] and partially protected monosaccharides [64]. The reactions are run without or in an inert solvent such as petroleum ether, benzene or THF with a dry inorganic base (Na_2CO_3 [63], K_2CO_3 [63], NaOH [64]) and a quaternary ammonium salt as catalyst. The work up is simple and yields are generally high.

Alcohols [2, 10, 69], amines [24, 70, 87, 146], carboxylic acids [2], thiols [2, 10, 79], nitro compounds [72] and others have been silylated with TMCS after prior conversion to a metal salt, but this method is only of preparative use in special cases. Metal salts of inorganic acids (e. g. LiI [73], NaN_3 [74, 75], alkali cyanides [76–79]) can also react with TMCS to yield the corresponding TMS-compounds. A method to produce N-Si or O-Si bonds is to form metal salts of amine or hydroxyl groups by deprotonation with a strong base such as BuLi [107, 108, 110], KH [111] or KOH [108]. The bis-silylation of primary amines, which cannot be achieved by silylation with TMCS/Et_3N, is possible by conversion of the amine into the metallised amide. Deprotonation of 4-bromoaniline with BuLi and treatment with TMCS gives the bis-silylated aniline in high yields [107]. Deprotonation of carbazole with n-BuLi or KOH and reaction of the Li/K-salt with TMCS in toluene, xylene or 1,2,3,4-tetramethylbenzene, results in the trimethylsilylated product [108]. Non-substituted β-sultames can be silylated with TMCS after metallisation with nBuLi in THF. The workup has to be done without water, because the product is very sensitive [110]. Sterically overcrowded pyrroles can be silylated with TMCS after deprotonation of 2,5-substituted pyrroles with butyllithium[114].

The technique of converting the substrate into a metal salt, which is subsequently reacted with TMCS, is widely applied for the preparation of silyl enol ethers and silyl ketene acetals from the corresponding metal enolates, especially Li-enolates (for comprehensive reviews on these and related reactions see references [36–39]).

"Kinetic" silyl enol ethers are selectively formed when a metal enolate, generated from a ketone and an alkali metal dialkylamide, is quenched with TMCS at low temperature. E. J. Corey and A. W. Gross [65] described an in situ trapping method and achieved higher selectivities than with the two-step procedure. If lithium tert-octyl-tert-butylamide is used as base, the regioselectivity is still higher than with lithium diisopropylamide and the E:Z ratio of the silyl enol ethers thus formed is likewise enlarged. The influence of the base on the product ratio has also been reported by K. Hattori and H. Yamamoto [117]. They used lithium diisopropylamide, lithium 2,2,6,6-tetramethylpiperidide and lithium hexamethyldisilylamide as base. The use of chiral lithium amide salts was studied by B. J. Bunn and N. S. Simpkins [118]. If bromomagnesium diisopropylamide is used for the generation of the enolate it is possible to prepare the "thermodynamic" silyl enol ethers under "kinetic" (non-equilibrating) conditions [66, 67].

A well elaborated procedure for the preparation of a silyl enol ether with LDA/TMCS in dimethoxyethane can be found in [68]. By using lithium bis(trimethylsilyl) amide as base, trimethylsilyl enol ethers are formed [122, 123]. The preparation of trimethylsilyl enol ethers has also been described by addition of NaI in the presence of Et_3N in a solvent (formation of trimethyliodosilane in situ). The syntheses of the two different enol ethers , which can be obtained from 1-methylcyclohexanone and 1methylcyclopentanone have been described in [119].

General studies on the silylation of simple aldehydes and ketones to form trimethylsilyl enol ethers in the presence of NaI have been published in [120]. The same silylation procedure has been shown in [121]. If ester enolates are trapped with TMCS, C-silylated products can be formed along with silyl ketene acetals (depending on sterical factors) [81, 82]. The preparation of trimethylsilyl ketene acetals from crotonic esters has likewise been shown in [124]. Similar results of C-silylated products have been achieved for N,N-dialkylamide enolates [83]. The E:Z ratio of the formed silyl ketene acetals can be influenced drastically by addition of HMPA to the reaction mixture [84].

Special synthetic methods are the silylation of ferrocene [125], reaction of O,O-diethyl-N-formylphosphoramidate [126] and the 1,4-bis-silylation of α, β unsaturated ketones with Pd-komplexes as catalyst [127]. TMCS-$InCl_3$ as a novel catalyst system has been described in [128]. Coupling of a base with ribose was reported in [129].

The C-trimethylsilylation of benzene and toluene with $AlCl_3$ as catalyst was carried out with low yields [130]. The preparation of 4-[(trimethylsilyl)methyl)]benzoic acid from p-toluoic acid and LDA [139], the silylation of $Cr(CO)_3$-indole komplexes [131], benzene derivatives [132], electrochemical reductive trimethylsilylation of aryl chlorides [133], the electrochemical synthesis of organosilicon compounds [137] and the silylation of activated olefins using a reactive metal anode [138] have been described.

Polyhalogenated biphenyls via Grignard reaction [134], thiophenes from 2-lithiothiophene [135], 2- and 4- chloropyridine to form 3-TMS-2,4-chloropyridine [136] have been silylated. 1-Methyl-3-trimethylsilyl-2-pyrrolidone was prepared by treatment of 1-methyl-2-pyrrolidone with sodium bis(trimethylsilyl)-amide and then with TMCS [141]. Silylation of propargyloxyethylchloride was carried out by treatment with lithium followed by TMCS [142]. Michael-like addition of Si groups to β-aryl-α, β-unsaturated carbonyl derivates with Si alkyl/$Bu_2Cu(CN)Li_2$ have been investigated in [143]. The silylation of isoquinoline by using Li/TMCS/TMCS is described in [144] with the formation of different products, e.g. 2,2'-bis-(trimethylsilyl)-1,1',2,2'-tetrahydro-1,1'-biisoquinoline. The same conditions have been used to silylate quinaldine and resulted in a mixture of two N-silylated products from the reductive silylation of the nitrogenous ring [145].

Typical procedures

Derivatisations without base are carried out without solvent. Preparation of TMS-nonaflate [89]:
Add dropwise 8.8 g TMCS (60 mmol) to 10.0 g (33.3 mmol) nonafluoro-1-butanesulfonic acid. HCl gas which forms immediately is allowed to escape. Stir the mixture at 50–70°C until no more gas is evolved (12 h). Additional fractional distillation gives the pure product.

Procedure with triethylamine as base, protection of tertiary alcohols [53]:
Add TMCS (0.1 mol) with stirring to a mixture of dry triethylamine (0.15 mol), the tertiary alcohol (0.1 mol), and DMSO, HMPA, DBU or imidazole (0.01–0.02 mol) in dry ether (200 ml). Keep the temperature of the mixture at 40°C by occasional cooling. After one hour, pour the reaction mixture into ice water (200 ml). After washing the ethereal solution with water, dry over $MgSO_4$ and evaporate. Fractional distillation gives the pure TMS-ether.

Trimethylsilyl ketene acetal from crotonic esters [124]:
Add crotonic ester (0.15 mol) in THF (25 ml) to a solution of LDA (0.165 mol) at –78°C, prepared in the usual way at 0°C from diisopropylamine (0.165 mol) in THF (200 ml) and n-butyllithium (0.180 mol) in hexane, (45 min) under nitrogen. After 60 min freshly distilled TMCS (0.375 mol) in the same solvent (25 ml) is added. Stir the reaction mixture for an additional hour, allow to come to room temperature, concentrate under vacuum, dilute with petroleum ether and filter. Distill the residue to obtain the pure product.

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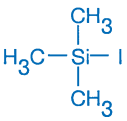

3.1.26 Trimethyliodosilane, TMIS

Trimethyliodosilane is one of the most reactive silylating agents, particularly useful for synthetic purposes. Although it has been known for many years, its chemical potential was discovered mainly in the last decade [1–3].

It has been used e. g. for the cleavage of ethers, esters, carbamates and ketals, for the synthesis of iodides, and as electrophilic catalyst in different reactions [1–3]. R. D. Miller and D. R. McKean were the first to use TMIS as silylating agent [4]. Later on, other authors showed its high silylating power by comparison with other silylating agents [5, 6].

Trimethyliodosilane is a clear, colourless liquid which is extremely sensitive to light and moisture.

Analytical applications

M. Donike and co-workers [7] found that trimethyliodosilane is by far the best catalyst for the quantitative silylation of hydroxyketosteroids with MSTFA. Hydroxyl groups are silylated immediately, keto groups yield the pure silyl enol ether within a few min (TMCS and potassium acetate are much less reactive; TMBS, although an excellent catalyst, needs longer reaction times and isomer formation is possible). The drawback with this application of TMIS is the formation of dehydrated products. This can be avoided by using only very small amounts of catalyst, by protecting from light and by addition of a very small amount of a reduction agent (e. g. cysteine or 1,4-dithioerythritol). M. Donike introduced this method for the determination of conjugated steroids in the routine urine analysis of anabolica [8].

Synthetic applications

R. D. Miller and D. R. McKean [4] found a mixture of HMDS/TMIS (1.1:1) to be a very efficient silylating agent for aldehydes and ketones. The thermodynamically controlled mixtures of trimethylsilyl enol ethers are generated at room temperature in very good yields. All γ- and δ-ketoesters (the ester groups are not affected!) [4], other ketoesters [18, 20], ketoamides [19] and α-halogenketones [9] can also be transformed regioselectively by this method to the corresponding silyl enol ethers. The utility of this method has also been described by other authors [10, 11]. H. H. Hergott and G. Simchen [5] compared the reactivity of ten electrophilic silylation agents in a system consisting of triethylamine and 1,2-dichloroethane for the silylation of ketones: trimethyliodosilane (together with TMS triflate) gave by far the highest reaction rates. Similar results on the silylating reactivity of TMIS were found by A. R. Bassindale and T. Stout [6].

N-(Trifluoroacetyl)lactams have also been shown to yield trimethylsilyl enol ethers by silylation with TMIS/Et_3N [15]. The preparation of trimethylsilylesters of acetate derivatives from the silver salt and TMIS in ether is possible in 29 % yield [16].The bis-silylation

of primary amines, especially N,N-bis-(trimethylsilyl)-cyclohexylamine was prepared by reaction of TMIS with the primary amine and Et_3N in different solvents. The best solvent with the highest yield is chloroform (65 % yield). Benzylamine and diisopropylamine are bis-silylated by this method as well. The authors describe the bis-silylated amine to be stable to water and alcohols in neutral and basic conditions and Grignard reactions [17].

D. Seebach and co-workers [12] described the mixture of TMIS/HMDS (2 : 1) in pyridine as a potent silylating agent for hindered hydroxyl groups (without base, alcohol reacts with TMIS to form the corresponding iodides by cleavage of the silyl ether intermediates! [1–3]). Transformation of a protected alcohol group (protected with tert-butyldimethylsilyl) to the corresponding iodine derivative was described in [21].

K. Kato and co-workers [13] prepared trimethylsilyl dithiocarboxylates by the reaction of an alkali dithiocarboxylate with a trimethylhalogensilane and found that the Cs-salt together with TMIS gave the highest reaction rates.

Besides its catalytic activity in the silylation of ketosteroids with MSTFA [7, 8], TMIS acts also as catalyst for the silylation with allyltrimethylsilane [14].

Special reactions with trimethyliodosilane are the preparation of mono and bis-silylated propynes from 1,3-bistrialkylstannylpropynes [22], the silylation of ketene diethylacetal with TMSI and Et_3N to trimethylsilylketene diethylacetal [23], the synthesis of (1-(trimethylsilyl)-alkylidene)triphenylphosphoranes [24], and the glycosylation of 5-substituted 6-azauracils with TMIS [25].

Typical procedures
Bis-silylation of amines [17]: N,N-Bis(trimethylsilyl)cyclohexylamine:
Dissolve N-trimethylsilylcyclohexylamine (0.1 mol) and Et_3N (0.1 mol) in 75 ml 1,2-dimethoxyethane. Then add TMIS (0.1 mol) dropwise under nitrogen. After stirring at 80°C for 6 h, evaporate the solvent in vacuo and treat the residue with ether (100 ml), 50 ml saturated $NaHCO_3$ solution and 50 ml water. Wash the ether phase with water, dry over Na_2SO_4 and distill. Yield: 40 %

Trimethylsilyl enol ethers [18]:
Add HMDS (1.6 mmol) and TMIS (1.3 mmol) at –20°C under nitrogen to a stirred solution of the ketone (0.4 mmol) in dichloromethane (2 ml), containing one piece of molecular sieve 4 Å. Stir the mixture under nitrogen for 15 min at –20°C and for 1 h at room temperature. After the reaction has come to completion, extract the reaction mixture with dry diethyl ether. Wash the extract with ice cooled saturated aqueous sodium hydrogen carbonate, dry over $MgSO_4$ and then concentrate. Elute the residue rapidly through a short alumina column with 4 drops of triethylamine in dry diethyl ether as eluant to obtain the pure silyl enol ether.

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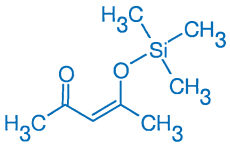

3.1.27 4-Trimethylsiloxy-3-penten-2-one, TMSacac

The trimethylsilyl enol ether of acetylacetone was shown by T. Veysoglu and L. A. Mitscher [1] to be a very potent silylating agent. Primary, secondary and even tertiary alcohols are silylated quantitatively in several min at room temperature without any catalytic assistance. The procedure can take place without solvent, however a polar solvent will increase the silylating potential.

Polyols and carbohydrates react slowly with TMSacac [2]. This disadvantage can be overcome by prior O-diethylborylation. Using this technique carboxylic acids can be silylated quantitatively as well [2]. 1,1-Dihydroxy compounds give alkylated products after reaction with TMSacac [3].

Analytical applications

A. T. Alekseev et al. [4] found TMSacac to be an efficient silylating agent with several advantages in gas chromatographic analysis:

- alcohols, phenols, mercaptans, carboxylic acids and aromatic amines are silylated rapidly at room temperature without catalyst. Nevertheless, if the reaction proceeds too slowly it can be accelerated by the addition of a catalytic amount of p-toluenesulfonic acid.
- the silylation potential is higher than that of BSA and BSA/TMCS
- TMSacac can be used for silylations if working with a selective thermionic detector sensitive to nitrogen-containing compounds is advisable
- acetylacetone, the only by-product of the silylation is volatile (bp 137°C).

TMSacac has also been shown to be a superior silylating agent for the preparation of silylated silica for bonded-phase chromatography [5]. K. D. McMurtrey showed, that the silylation potential of TMSacac in the reaction with silica gel under conditions useful for end-capping HPLC bonded phase packings lies between TMCS and HMDS. Additionally, seven trimethylsilyl donors have been studied [6]. The derivatisation of an organic acid, an alcohol, two amines of different relative molecular mass, a thiol and a phosphite with different derivatising agents have been carried out and their reaction with TMSacac and with or without pyridine or 4-dimethylaminopyridine is described in [7].

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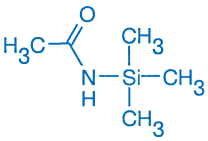

3.1.28 N-(Trimethylsilyl)acetamide, TMS-acetamide

TMS-acetamide is the silylamide with the poorest silylation potential [1, 2, 3]. L. Birkofer and co-workers [4] demonstrated its utility in the silylation of carbohydrates by melting them with solid TMS-acetamide [4, 5] or by refluxing both components in pyridine solution [4, 6].

TMS-acetamide is less useful than MSA or BSA for the silylation of amino acids [7] but has been employed for the silylation of cholesterol [8], cefamandol [9], 6-amino-penicillanic acid [10] and 3,4dioxo-2,5-dihydrobenzoic acid [11].

Alcohols were silylated by using TBAF as catalyst [16]. Allylic alcohols react with TMS-acetamide [12, 13] under mild conditions (e.g. refluxing in pentane [13] or by stirring in a solution of pyridine for 27 hours [15]).
It has also been used for the in situ mono silylation of primary amines [14].

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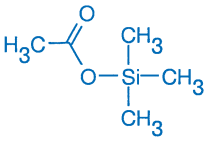

3.1.29 Trimethylsilyl acetate

Trimethylsilyl acetate is a rarely used silylating agent. It was described for the silylation of hydroxyl-group-containing compounds in a patent [1] and for the quantitative silylation of alcohols [2]. The silylation of carboxylic acids with respect to electronic and steric effects has been examined [3]. Compared to other electrophilic trimethylsilylating agents, trimethylsilyl acetate has a very low silylation potential (TMCS) [4].

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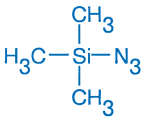

3.1.30 Trimethylsilyl azide

Trimethylsilyl azide is a very valuable reagent in synthetic chemistry (e.g. for 1,3-dipolar cycloaddidions [1, 2], preparation of isocyanates etc. [3, 4, 7]). It is also a reactive silylating agent and has been used for the silylation of hydroxyl compounds in the xanthone and coumarin series [5]. It was described as silylating primary and secondary alcohols and phenols very rapidly and efficiently at room temperature [6, 8]. Tertiary alcohols do not react under the reaction conditions employed. The only by-product of this mild silylation method is gaseous HN_3.

Propenoyl trimethylsilane reacts with trimethylsilyl azide to give the 3-azido-1-trimethylsiloxy-1-trimethylsilyl-propene [9]. Substitution of methoxy groups by azido groups in derivatives can be carried out with trimethylsilyltriflate as catalyst [10]. Glycosyl azides from peracylated sugars are synthesised in high yields with diverse catalysts [11]. T. Mukaiyama et al. [12] used the reaction of ribofuranose derivatives with trimethylsilylazide in the same kind of reaction and with the same catalysts as in [11]. R. Neidlein and P. Meffert have described the synthesis and chemical reactions of new azide derivatives [13].

Typical procedure

For the silylation of secondary alcohols [8]: Add trimethylsilyl azide (0.1 mol) at 25°C under nitrogen to a solution of the alcohol in dry THF (30 ml). Stir the mixture for 2 h and evaporate. Upon distillation, the residue gives the silylated derivative (50 %).

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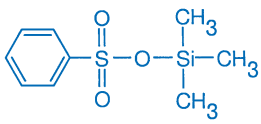

3.1.31 Trimethylsilyl benzensulfonate

G. Simchen and co-workers [1] compared the silylation potential of trimethylsilyl benzenesulfonate for the silylation of ketones, with nine other electrophilic silylation agents. It was found to react about 160 times faster than TMCS but much slower than TMS triflate and TMIS.

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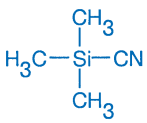

3.1.32 Trimethylsilyl cyanide, TMSCN

TMSCN is a valuable reagent in synthetic chemistry (e.g. preparation of silylated cyanohydrins, acyl cyanides etc.) [1–5]. It was described as a useful and reactive silylating agent for carboxylic acids and alcoholic and phenolic hydroxyl groups [6]. The preparation of a bridgehead silyl ether by silylation of an alcohol group without a base and by heating can be accomplished as well [7]. Amines and thiols react more slowly, amides, ureas and carbamates do not react at all [6]. Silylation takes place at room temperature without any solvent and with evolution of hydrogen cyanide (heating is necessary for amines and thiols; with carbohydrates, a small amount of DMF is used to solubilize the substrates). The reactivity of TMSCN toward a sterically hindered hydroxyl compound (2,6-diphenylphenol) was compared with other silylating agents and the following order was found:

BSA > TMSCN > TMS triflate > bis(trimethylsilyl)sulfamide > HMDS > TMSO > TMCS/Li_2S > TMCS/base.

Silylation of amino acids with TMSCN was carried out by treatment of amino acids or even their amine salts [8]. Bis(trimethylsilyl)methylamine has been prepared by the reductive silylation reaction of TMSCN with TMCS and Li, in the presence of HMPA [11, 17]. The opening of epoxide rings can be carried out with TMSCN and zinc iodide to give the 1-trimethylsiloxy-2-cyano-derivative [18].

Aldehydes and ketones react efficiently with TMSCN to produce the corresponding 2-(trimethylsilyl)oxy alkyl nitriles by employing ZnI_2 [9]. This procedure can be used for protection of the carbonyl group [10]. Succinyl chloride and TMSCN react to form succinyl dicyanide in 7 days [12]. In special reactions, TMSCN was used for the synthesis of cyanides from alcohols and methylethers via substitution of an alcoholic or methoxy group (e. g. in acetals) [13–16].

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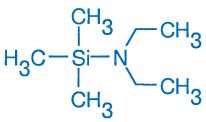

3.1.33 N-(Trimethylsilyl)diethylamine, TMSDEA

TMSDEA is a strongly basic silylating agent with moderate silylation power (greater than HMDS/TMCS, less than BSA, BSTFA, MSTFA). It is useful for analytical and preparative purposes, silylating most functional groups. Its by-product, the highly volatile diethylamine (bp 55°C) elutes very early in GC and can be easily removed by distillation in preparative procedures. K. Rühlmann was the first to use TMSDEA for silylation (amino acids) [1, 2].

Analytical applications

TMSDEA has been used for the silylation of various functional groups [3–7]. It is particularly useful for the silylation of low molecular weight acids and all kinds of amino acids [1, 2, 8–11, 14]. It often serves as its own solvent and its silylation potential can be increased by addition of an acidic catalyst (TMCS [8, 11, 15, 16, 35], trichloroacetic acid [8], silica-alumina [8, 9], ammonium sulfate [10]).
A mixture of TMSDEA with BSTFA, TMCS and pyridine (30 : 99 : 1 : 100) has been shown to be useful for the simultaneous silylation of acidic, neutral and basic metabolites of tyrosine and tryptophan [11].

Methylolmelamines have been selectively O-silylated by TMSDEA and analysed by gel permeation chromatography (BSA leads to mixtures of higher silylated products) [12].
For methylolated urea-formaldehyde reaction products, TMSIM is necessary to achieve a selective O-silylation, whereas TMSDEA gives mixtures of mono-, bis- and tris-silylated products [13].

Comparative data with other silylating agents are given for amino acids [8, 9, 11, 15], steroids [15], urea-formaldehyde reaction products [13], hypoxanthine and guanine [16], and for different functional groups [17].

Synthetic applications

Although TMSDEA is not a very common preparative agent there are some very interesting applications. I. Weisz et al. [18] have found that TMSDEA is very sensitive to the steric environment of hydroxyl groups and selectively silylates equatorial hydroxyl groups. Axial hydroxyl groups are not affected.
This approach has found considerable use in prostaglandin synthesis [19–22]).
A. Ricci and co-workers showed that TMSDEA is the best reagent for the silylation of γ-crotonolactone [23] and its sulfur and nitrogen analogues [24], yielding the corresponding silyl enol ethers. Moreover TMSDEA has been used for the silylation of amino acids [1, 2, 14, 30], dipeptides [14, 25], amines (catalyst: $(NH_4)_2SO_4$) [10, 26], aminophenols [27], aminobenzenethiol [28], phenylhydrazine (disilylation, catalyst $(NH_4)_2SO_4$) [29], iminodiacetic acid (trisilylation) [30], benzimidazole [31] and alcoholic hydroxyl groups in simple [10, 32] and complex molecules [33, 34, 39, 40, 41].

The N,N'-disilylation of α,ω-diaminoalkanes (catalyst: TMCS) [35], the disilylation of ammonium alkyl hydrogen phosphates [36], the trisilylation of glycine [37] and the silylation of methylphenyl sulfoximine [38] have been described. Propenoyl trimethylsilane reacts with TMSDEA to give the 3-(N,N-diethylamino)-1-trimethylsiloxy-1-trimethylsilyl propene [42].

Typical procedures

Synthesis of N,N-bis-trimethylsilylamines with TMSDEA [10]:
Treat 0.4 mol amine with TMSDEA (0.84 mol) and add traces of $(NH_4)_2SO_4$. Then heat the reaction mixture and distill the generated diethylamine continuously. After several hours, distill the residue to obtain the pure product.

Derivatisation of aromatic carboxylic acids or low molecular weight aliphatic acids in GC sample preparation:

1. Combine 5–10 mg of aromatic carboxylic acid or low molecular weight aliphatic acid and 200–300 µl of TMSDEA in a 1 ml Reacti-Vial™ miniature reaction vial.
2. Vent Reacti-Vial™ miniature reaction vial with a luer needle. Heat to 60°C for 15–20 min.
3. Analyse by gas chromatography.

If necessary, a volatile solvent, such as acetonitrile (or an alternative) may be used.

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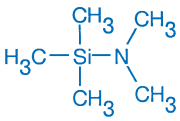

3.1.34 N-(Trimethylsilyl)dimethylamine, TMSDMA

TMSDMA has approximately the same silylating properties as TMSDEA and can be used for identical purposes. Its lower boiling point and gaseous reaction by-product, dimethylamine, are the main advantages of TMSDMA compared to TMSDEA. TMSDMA is also useful for the silylation of silica gel and glass surfaces [1].

Analytical applications

Similarly to TMSDEA, TMSDMA is particularly useful for the silylation of low molecular weight acids, especially amino acids [2]. Its silylation potential can be increased by an acidic catalyst such as TMCS [3–5]. H. Iwase and co-workers have shown that it silylates hypoxanthine and guanine [4] rapidly and efficiently.

Synthetic applications

TMSDMA with 10 % TMCS has been found to be the reagent of choice for the silylation of urea-formaldehyde polycondensates. TMSDEA, BSA and TMSIM give lower yields [5]. Furthermore, it has been used for the silylation of hydroperoxides [6], oximes [7], sterically hindered N-alkylcyanamides [8] and alcoholic hydroxyl groups [9–11]. Bicyclic ketones give silyl enol ethers in good yields when the silylation is catalysed by p-toluenesulfonic acid [12], whereas normal aldehydes and ketones form dimethylaminoenamines under these conditions [13]. α-Chloroethers react with TMSDMA to give the Mannich-reagent (N,N-dialkyl iminium chlorides) [14]. Phosphorus(III)-trimethylsilylesters were synthesised by the silylation of appropriate phosphorous acid compounds with TMSDMA. By using HMDS as silylating agent, the reaction stopped at the monoester step [15].

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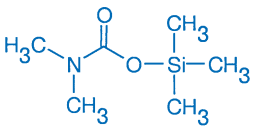

3.1.35 Trimethylsilyl N,N-dimethylcarbamate, DMCTMS

DMCTMS was described by D. Knausz and co-workers [1] as being an efficient silylating agent for alcohols, phenols and carboxylic acids. The following advantages make it useful for the synthetic and particularly the analytic chemist:

- the silylation is a non-equilibrium reaction because CO_2 evolves from the system
- the second by-product, dimethylamine, is very volatile
- the silylation is autocatalytic, catalysed dy the dimethylamine formed [5].

Synthetic applications

Trimethylsilyl N,N-dimethylcarbamate is a reagent for silylation of alcohols (primary [1], secondary [1] and tertiary [1, 5]) in 64–91 % yields, phenols in 56–94 % yield and carboxylic acids (aliphatic and aromatic) in 78–87 % yield. It reacts with acid halides, carboxylic anhydrides, dicarboxylic anhydrides [1], chloroformates and lactones [3].

Analytic applications

E. Csató et al. [2] compared DMCTMS with BSTFA in the silylation of ribonucleosides and found it to be a very effective silylating agent. It is also a suitable solvent for nucleosides and can be used as such. DMCTMS can likewise be used advantageously for the silylation of alkaloid salts without previous liberation of the base [4]. In the case of ephedrine, O- and N-silylation takes place. DMCTMS can not be applied to the silylation of compounds containing oxo groups because of enamine formation.

Typical procedure

Silylation of alcohols, phenols and carboxylic acids [1]:
Place the compound to be silylated in a three-necked round-bottom flask equipped with a stirrer, a reflux condenser, a drying tube, and a dropping funnel. Add trimethylsilyl N,N-dimethylcarbamate (10 % excess) while stirring. The start of the reaction is in-dicated by evolution of carbon dioxide and is generally complete within 3 to 5 min. However, longer times and/or higher temperatures may be needed in the case of compounds containing bulky hindered groups. The products can be purified by distillation.

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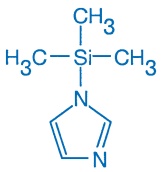

3.1.36 1-(Trimethylsilyl)imidazole, TMSIM

TMSIM, first prepared by L. Birkofer and A. Ritter [1], is one of the most powerful silylating agents for hydroxyl groups [2–6]. However, unlike similarly reactive silyl amides (MSTFA, BSTFA, BSA), it does not react with aliphatic amines [7–9] (less basic amines and amides may react with TMSIM [10]). This selectivity, together with its high reactivity, makes TMSIM a widely used silylating agent especially for analytical purposes.

Analytic applications

TMSIM has been used for the silylation of all kinds of hydroxyl groups [2, 6]. Carboxyl groups [12, 13], thiols [10, 54], less basic amines (e. g. aniline [10]), indole derivatives [11], amides (e. g. sulphonamides [10]), and imides (e. g. phthalimide [10]) are also silylated. TMSIM is particularly useful for highly hindered hydroxyl groups and for polyfunctional molecules containing basic amino groups where in the most cases only a single derivative is formed.

The silylation procedure works normally in pyridine, sometimes in acetonitrile, ethyl acetate or other solvents, or even without solvent. "On column" derivatisation [14] and vapor phase silylation [15] can likewise be carried out with this reagent.

TMSIM is mostly used without a catalyst, nevertheless the silylation rate can be increased in some cases by addition of a catalyst such as TMCS for the silylation of steroids[16], dammarane-type triterpene triols, tetrols and ketoalcohols[17], and trichothecenes [18, 19]. Pyridine hydrochloride is used for the silylation of steroids, trifluoroacetic acid [21] (silylation of phenols), O-methylhydroxylamine hydrochloride [20, 22, 56] for the silylation of sterically hindered hydroxyl compounds, piperidine [23] for prostaglandin-E methyl esters and potassium acetate [24] for ecdysterone.

Mixtures of TMSIM with other silylating agents are very popular as they provide potent universal silylating reagents. The most

important mixtures are BSA/TMSIM/TMCS (3:3:2) [16, 18, 25] and BSTFA/TMSIM/TMCS (3:3:2) [26, 27]. These mixtures are available from Fluka as ready-to-use silylating mixtures (see the section on "silylating mixtures"). M. Donike [28] proposed a mixture of MSTFA/TMCS/TMSIM (100:5:2) for the determination of free steroids in the routine analysis of anabolica. TMSIM is also a very efficient catalyst for the silylation of indolic NH with MSTFA [29] or BSTFA [30].

A variety of references on the applications of TMSIM in the analysis of different, mostly OH-containing compounds (especially carbohydrates, steroids and other natural compounds), can be found in the literature [2–6]. Some important references are cited here for the silylation of the following classes of substrates: lower fatty acids [12, 13], low molecular weight alcohols [10, 15], octadecanoic acid, octadecan-1-ol, octadecylamine, N-methyloctadecylamine, octadecane-1-thiol, dioctadecylphosphite (silylation with TMSIM alone or with pyridine [59], carbohydrates [31–34, 40, 41], triterpentriols and tetrols [17], urea-formaldehyde reaction products (for gel chromatography) [35], steroids [16, 22, 24, 25, 26, 36, 37], prostaglandins [63], trichothecenes [18, 19, 27, 42] sugars [61, 64] and the silylation for studies on the metabolism of anabolics.

Comparative data to other silylating agents are given for steroids [16, 22, 36, 37], nucleic acid compounds [38, 39], trichothecenes [18, 27] and miscellaneous compounds [10]. Also the reactivity of TMSIM with 6 other trimethylsilyldonors in reaction with silica gel has been studied [60]. Thus, TMSIM is the strongest silylating agent, stronger than TMSDMA or BSTFA.

Synthetic applications
TMSIM has been used for the mild, selective silylation of alcoholic hydroxyl groups [43–50, 57]. The reaction proceeds normally in an inert solvent (e.g. CCl_4, THF) at room temperature without catalyst (nevertheless the addition of a catalyst such as TMCS [50] or pyridine [44] is possible). Dopamine hydrochloride has been selectively O-silylated by TMSIM without solvent [9]. Carbonyl compounds, in which the enol form is stabilised by conjugation give the silyl enol ethers in high yields by silylation with TMSIM [51] or HMDS/imidazole ("TMSIM in situ") [52]. Common ketones can be transformed to the silyl enol ethers regio- and stereoselectively by reaction of the corresponding enol boranes with TMSIM [53]. Thiols [54], primary amines (silylation in situ without isolation) [58] and amides [55] can also be silylated by TMSIM in some cases.
Propenoyl trimethylsilane reacts with TMSIM to 3-(N-imidazolyl)-1-trimethylsiloxy-1-trimethylsilyl-propene, a functionalised silyl enol ether [61].

Typical procedure
Silylation of alcoholic hydroxyl groups [57]: Add TMSIM (216 mmol) at 0°C to a solution of the alcohol (173 mmol) in 100 ml petroleum ether. After stirring for about 12 h, filter off the formed imidazole. Wash the filtrate several times with 100 ml of saturated aqueous NH_4Cl solution until the pH of the solution remains slightly acidic. Extract the combined aqueous phases twice with 50 ml of petroleum ether, and wash the combined organic phases with 150 ml of brine. After drying over $MgSO_4$, concentrate the solution and fractionate the residue.

For the silylation of hydroxyl groups on highly hindered steroids and other hydroxyl and carboxyl group containing compounds (amines are not effected) in sample preparation for GC, refer to [63].
1. Combine 10–15 mg of sample and 1.0 ml TMSI in pyridine in a 3 ml Reacti-Vial™ miniature reaction vial.
2. Shake to dissolve, sample may be heated to 60–70°C if needed. Silylation is complete upon dissolution.
3. Analyse by gas chromatography.

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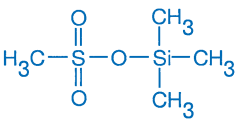

3.1.37 Trimethylsilyl methanesulfonate

G. Simchen and co-workers [1] compared the silylation capacity of trimethylsilyl methanesulfonate in the silylation of ketones with nine other electrophilic silylating agents. With triethylamine as base and in 1,2-dichloroethane as solvent, it was shown to react about 40 times faster than TMCS but much slower than TMS triflate and TMIS.

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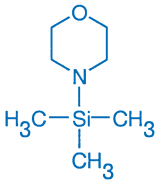

3.1.38 4-(Trimethylsilyl)morpholine

4-(Trimethylsilyl)morpholine has been evaluated by R. Piekos [1] as silylating agent for different functional groups. It shows good silylating properties but its silylation potential was found to be lower in most cases than that of BSA or TMSIM.

Reference

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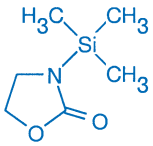

3.1.39 3-Trimethylsilyl-2-oxazolidinone, TMSO

TMSO has been shown by A. L. Palomo [1, 8] and C. Palomo [2–6] and co-workers to be a very efficient and powerful silylating agent for sulfonic acids, carboxylic acids, amino acids, alcohols, thiols and 1,3-dicarbonyl compounds. The use of TMSO has been described for analytical purposes (silylation of hindered alcohols and phenols).

Analytical applications

G. W. Perold [7] described TMSO as a highly useful reagent for the efficient silylation of phenols and hindered alcohols for GC-analysis. Silylation takes place in DMF or pyridine with p-toluenesulfonic acid as catalyst (p-toluenesulfonic acid was chosen as catalyst instead of TMCS because the latter attacks plastic fitments aggressively under forced reaction conditions).

Synthetic applications

Trifluoromethanesulfonic acid has been silylated with TMSO without solvent [8]. Carboxylic acids can be silylated quantitatively by TMSO in CCl_4 without any catalyst [2] (this silylation can also be catalysed by acids [6] or bases [1]). The by-product (2-oxazolidinone), which is chemically very inert, can be easily removed by filtration. This method is particularly useful for substituted malonic acids which readily undergo decarboxylation [2]. 1,3- Dicarbonyl compounds (basic catalysis) [3], alcohols (acidic catalysis) [4, 6], amino acids [5] and thiols (acidic or basic catalysis [6]) are silylated very efficiently by TMSO under very mild conditions. Even highly hindered alcohols are rapidly silylated [4, 6].

Typical procedure

Silylation of carboxylic acids [2]:
Add TMSO (16 ml, 105 mmol) to a solution of the carboxylic acid (100 mmol) in tetrachloromethane (50 ml) and heat the mixture to reflux temperature for 15–20 min. Then cool to 0–5°C and filter off the precipitated 2-oxazolidinone in the absence of moisture. Evaporate the solvent and distill the crude product.

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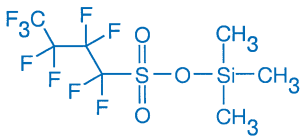

3.1.40 Trimethylsilyl perfluoro-1-butanesulfonate, TMS-nonaflate

TMS-nonaflate is, like TMS triflate, one of the strongest silylating agent. It was used as highly selective Friedel-Crafts catalyst for nucleoside formation from silylated heterocycles and peracylated sugars with much higher yields than other silylating procedures [1].

1,3-Dithietane-1,1,3,3-tetroxide was silylated with TMS-ONf in the presence of triethylamine yielding 2,4-bis(trimethylsilyl)-1,3-dithietane-1,1,3,3-tetroxide, 2,2,4-tris(trimethylsilyl)-1,3-dithietane-1,1,3,3-tetroxide and 1-trimethylsiloxy-2,4,4-tris(trimethylsilyl)-1,3-dithiet-1-ene-1,3,3-trioxide which can be considered as the first enol ether of a sulfone [2, 3]. Iodosobenzene reacts with Me_3SiX to form, by a single step reaction, mixed iodosobenzene sulfonates $PhI(X)OSO_2R$, an unsymmetrical tricoordinate iodinane [4].

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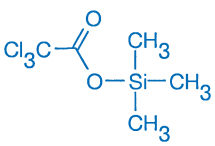

3.1.41 Trimethylsilyl trichloroacetate

Trimethylsilyl trichloroacetate was proposed for salt-free silylation of phenols, thiols, carboxylic acids, amides, cyclic carbamates, β-keto esters and acetylenes [1]. The silylation takes place in the presence of a catalytic amount of potassium carbonate/18-crown-6 at 100–150°C, producing trichloromethane and CO_2 as by-products. The reaction time is less than one hour, the yields are between 75 and 94%. Aldehydes and ketones yield trimethylsilyl trichloromethyl carbinols rather than silyl enol ethers. It was also shown that amines can be silylated by the same method [2].

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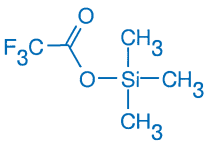

3.1.42 Trimethylsilyl trifluoroacetate

Trimethylsilyl trifluoroacetate has not yet been used for silylating purposes but promises to be a useful silylating agent with a silylation potential stronger than that of trimethylsilyl acetate and trimethylsilyl trichloroacetate.