Helmut Vorbrüggen

Silicon-mediated Transformations of Functional Groups

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H. Vorbrüggen

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Silicon-mediated Transformations of Functional Groups

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Library of Congress Card No.: applied for
A catalogue record for this book is available from the British Library.

Bibliographic information published by Die Deutsche Bibliothek
Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available in the Internet at <http://dnb.ddb.de>.

Printed in the Federal Republic of Germany
Printed on acid-free paper

Cover Design 4t Matthes+Traut, Werbeagentur GmbH
und T. Borosch, Technische Universität Darmstadt
Typesetting K+V Fotosatz GmbH, Beerfelden
Printing Strauss GmbH, Mörlenbach
Bookbinding Litges & Dopf Buchbinderei GmbH, Heppenheim

ISBN 3-527-30668-4

Contents

Preface

About 30 years ago we had at Schering AG the need of synthesizing a series of N^4-substituted cytidines and N^6-substituted adenosines as potential antiviral and biologically active compounds. Because the hitherto used conventional methods of synthesizing such compounds implied at least four reaction steps, we looked for new methods and discovered that just heating of uridine or thymidine with excess hexamethyldisilazane, $Me_3SiNHSiMe_3$, (HMDS) in the presence of ammonia, primary and secondary amines not only O-silylates and thus protects the hydroxyl groups in the ribose moieties but also silylates-activates the O^4-oxygen function in uridines, which is aminated to give in one reaction step the corresponding persilylated cytidines as well as persilylated water = hexamethyldisiloxane, $Me_3SiOSiMe_3$, (HMDSO). The O-$SiMe_3$ protecting groups in the ribose moieties are subsequently removed by *in situ* transsilylation with added excess boiling methanol, whereupon the free cytidines crystallize out in high yields. Analogously, the O^6-oxygen functions in inosine, guanosine or xanthosine are silylated-aminated in the presence of catalytic amounts of Lewis acids to the corresponding N^6-substituted persilylated adenosines, which give on transsilylation with boiling methanol the corresponding biologically active free crystalline adenosines in high yields.

Thus encouraged, we applied this principle of silylation-activation of oxygen functions to a number of aliphatic as well as heteroaromatic systems followed by subsequent or concomitant nucleophilic substitution e.g. with amines, cyanides, halides or hydrides while removing water as HMDSO. Although we could investigate only a rather limited range of such reactions, we were pleased to note that this principle of silylating-activating oxygen functions followed by nucleophilic substitution has subsequently been more and more frequently applied by other groups as discussed in detail in this review.

Thus we hope that these O-silylations-activations with the readily available HMDS ($Me_3SiNHSiMe_3$), TCS (Me_3SiCl), dimethyldichlorosilane (Me_2SiCl_2), hexamethylcyclotrisilazane $(HNSiMe_2)_3$, OMCTS $(HNSiMe_2)_4$, tetra(alkoxy)silane $(Si(OR)_4)$ or silicon tetrachloride ($SiCl_4$), most of which can also effect the transient protection of any present hydroxyl group, and the subsequent or concomitant reaction with nucleophiles accompanied by formation of silylated water as HMDSO ($Me_3SiOSiMe_3$), $(OSiMe_2)_n$ or SiO_2 will be applied more often in the fu-

ture to those numerous reactions in preparative organic and inorganic chemistry, in which water is being eliminated.

Acknowledgements

I want to thank in particular my former excellent collaborators Mr. K. Krolikiewicz and Mrs. B. Bennua-Skalmowski at Schering AG as well as my former graduate students Drs. D. Bohn, W. Bühler and M. Marschner for all of their work. I am furthermore obliged to my colleagues Drs. H. Künzer and S. Hecht for reading and commenting on part of the manuscript!

The writing of this review during the last years after my retirement from Schering AG in 1995 as well as some connected experimental work would not have been possible without the generous hospitality extended to me by my colleagues Professors H. H. Limbach, J. Mulzer, H.-U. Reissig and A. D. Schlüter at the Department of Organic Chemistry of the Free University of Berlin, where a laboratory and an office was made available to me in 1995. My work on silylation-amination was furthermore supported by a generous gift of hexamethyldisilazane (HMDS) from Bayer AG, of hexamethylcyclotrisilazane from K. Bucher GmbH and of other chemicals from Schering AG.

Last but not least, I want to thank my wife for her understanding and patience with me spending many hours with the manuscript of this review either at home or at our seaside retreat in summer.

Berlin H. Vorbrüggen
June 2004

1
Introduction

Many common synthetic reactions in preparative organic chemistry, for example amide (peptide or polyamide synthesis), aliphatic, or heteroaromatic amidine, or guanidine syntheses and ester and ketal (glycoside) formation or Stobbe and Claisen–Schmidt condensations involve the generation of water, which usually has to be removed to achieve clean and quantitative conversions. Because of its high heat of evaporation removal of water, e.g. during esterification by azeotropic distillation with solvents such as benzene [1], toluene, or xylene, usually implies extended heating in the presence of Lewis acids, bases, or molecular sieves, which often causes side reactions or partial decomposition of the desired end products. Because of these inherent problems associated with removal of water during chemical reactions, any new technique for activating reaction partners and of eliminating water in the form of new simple derivatives is of general interest.

Whereas almost all organic chemists are familiar with the different aspects of silylation for protection of functional groups [2–6], the concept of *protecting* any alcoholic or phenolic hydroxyl groups present by *silylation* while simultaneously *silylating–activating* [2, 7] suitable amide, lactam, imide, urea, carboxyl, nitro, or sulfoxide groups or hydroxy-*N*-heterocycles such as uracils, imidazolones [7], or 1,2,4-triazolones [7] as well as benzylic or allylic hydroxyl groups [8, 9] (cf. Scheme 1.1) should always be kept in mind. The activated silylated intermediates that can react with nucleophiles, such as amines, or electrophiles, such as acid chlorides, under rather mild reaction conditions with elimination of the very non-polar and volatile persilylated water (=hexamethyldisiloxane, $Me_3SiOSiMe_3$, HMDSO, **7**, b.p. 100 °C) instead of the polar water or of Me_3SiCl **14** instead of HCl, are only gradually entering common chemical knowledge. The included table of sources of surprisingly cheap

[1] N. S. Barta, K. Paulvannan, J. P. Schwarz, J. R. Stille, Synth. Commun. **1994**, *24*, 583
[2] L. Birkofer, A. Ritter, Angew. Chem. **1965**, *77*, 414
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[4] B. E. Cooper, Chem. Ind. **1978**, 794
[5] G. van Look, Fluka Chemika, Silylating Agents, **1988**, 9–105
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[7] L. Birkofer, P. Richter, A. Ritter, Chem. Ber. **1960**, *93*, 2804
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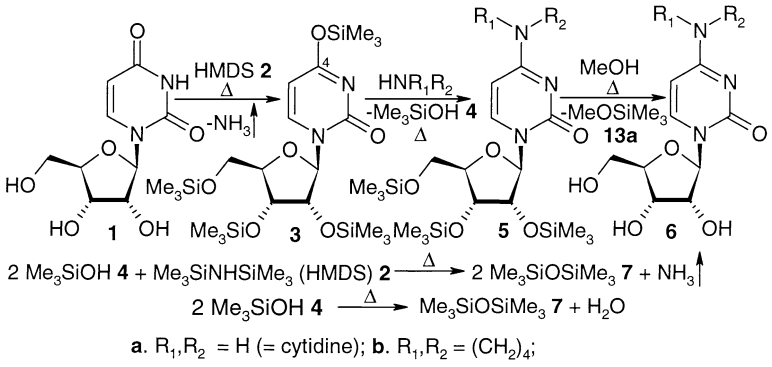
[9] M. Akita, H. Yasuda, A. Nakamura, Bull. Chem. Soc. Jpn. **1984**, *57*, 480



Scheme 1.1

silicon chemicals should convince chemists in development and production that this chemistry is also suited to any large scale synthesis.

We became involved in silylation–activation–amination ca. 30 years ago while trying to simplify the amination of uridine **1** to modified cytidines **6** [10, 11] (Scheme 1.1), which using conventional procedures requires at least three or four reaction steps (cf. Section 4.2.3). In the first cytidine synthesis 2′,3′,5′-tri-*O*-acetyl-4-*O*-ethyluridine (cf. compound **211** in Section 4.2.3) was converted on heating with ammonia into cytidine **6a** and ethanol as the leaving group [12]. Because the UV spectrum of 2′,3′,5′-tri-*O*-acetyl-4-*O*-ethyluridine **211** is very similar to that of persilylated uridine **3**, which is readily obtained from uridine **1** by heating with hexamethyldisilazane (HMDS) **2**, we heated uridine **1** with excess hexamethyldisilazane (HMDS) **2**, whereupon NH_3 is evolved, and excess primary or secondary amines, without solvent, to give, in a one-step/one-pot reaction, persilylated uridine **3**, followed by addition of the amines to the activated 4-position of **3** (cf. structure **214** in Scheme 4.15 in Section 4.2.3) and, after elimination of trimethylsilanol **4** as the leaving group, the persilylated cytidines **5** [10, 11]. The leaving group trimethylsilanol **4**, which is more acidic [13] (cf. Section 3.1) and thus much more reactive than *tert*-butanol, is silylated *in situ* by excess hexamethyldisilazane (HMDS) **2** to the rather non-polar hexamethyldisiloxane (HMDSO) **7** and ammonia, which escapes at normal pressure. Thus elimination of the polar water in these aminations is replaced by elimination of persilylated water (=$Me_3SiOSiMe_3$, HMDSO, **7**). Because trimethylsilanol **4** and the water, which is formed by the acid- or base catalyzed dimerization of two equivalents of trimethylsilanol **4** to hexamethyldisiloxane **7** [14], can deactivate the activated 4-trimethylsilyloxy group in **3** to give deactivated 2,3,5-*O*-silylated uridine and HMDSO **7**, silylation of trimethylsilanol **4** by excess hexam-

[10] H. Vorbrüggen, K. Krolikiewicz, U. Nieballa, Angew. Chem. Int. Ed. **1971**, *10*, 657
[11] H. Vorbrüggen, K. Krolikiewicz, U. Nieballa, Liebigs Ann. Chem. **1975**, 988
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[14] W.T. Grubb, J. Am. Chem. Soc. **1954**, *76*, 3408

ethyldisilazane (HMDS) **2** to hexamethyldisiloxane (HMDSO) **7** is mandatory to achieve high yields. To shift all these equilibria to the right it is, furthermore, optimum for preparative scale silylation–aminations employing higher boiling amines (b.p. > 120–130 °C), to remove hexamethyldisiloxane (HMDSO) (b.p. 100 °C) [15] or its azeotrope (b.p. 89–91 °C) [13] with trimethylsilanol **4** (b.p. 99 °C) (cf. Section 2.1) by distillation over a short Vigreux column during the reaction.

After silylation–amination *in situ transsilylation* (cf. Section 2.3) of the intermediate persilylated cytidines **5** with excess boiling methanol for 3–5 h gives the desired free cytidines **6** and methoxytrimethylsilane **13a** (b.p. 57 °C) [13]. Thus *protection* of the alcoholic hydroxyl groups of the ribose moiety and *silylation–activation* of the 4-position in the pyrimidine moiety in persilylated uridine **3**, and the concomitant *amination* of **3**, all in one reaction step, to **5** is followed finally by *in situ transsilylation* (cf. Section 2.3) with excess boiling methanol in one reaction vessel. All these steps proceed to afford free or N^4-substituted crystalline cytidines **6** in high yields [11] (cf. the preparation of N^4(tetramethylene)cytidine **6b** in 95.4% yield in Section 1.1.). This simple one-pot reaction is also very easy to perform on a technical scale, as are the subsequently discussed analogous silylation–aminations of purine nucleosides and other hydroxy-*N*-heterocycles (cf. Sections 4.2.4 and 4.2.5). The concept of silylation–activation while simultaneously *protecting* hydroxyl groups in alcohols, phenols, or phosphoric acids by silylation was subsequently "rediscovered" and appropriately termed "*transient protection*" [16–18].

Most of the other silylation–activation–substitution reactions reported in this review are mechanistically related. Several new reactions (such as those discussed in Sections 7.1, 7.2, and 7.4) have been discovered by following these lines of thinking about activation of functional groups by *O*-silylation and subsequent or concomitant reaction with nucleophiles giving the expected products and hexamethyldisiloxane **7**. It can thus be expected that current and new *silylation–activation reactions* will be more commonly used in preparative chemistry in the future.

In retrospect, the first review [19] on the subsequently discussed *mobility* of trimethyl- or other trialkylsilyl groups (cf. Section 2.4), which discusses the equilibrium between the *N*-silylated form **8** and the *O*-silylated form **9** of the 6,7-benzocaprolactam as determined by ^{1}H NMR, (Scheme 1.2) should have drawn general attention to this field, because **9** is a reactive *O*-trimethylsilyl iminoether, which can be expected to undergo addition–elimination reactions of nucleophiles Nu–H or Nu–$SiMe_3$, in particular in the presence of Lewis acids to give **10** and trimethylsilanol **4** as the leaving groups and, eventually, HMDSO **7**. Likewise, the *N*- or *O*-trimethylsilyl groups in the subsequently discussed *N,O*-bis(trimethylsilyl)acetamides or formamides **22** can be assumed to be in equilibrium [19].

---

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[16] G.S. Ti, B.L. Gaffney, R.A. Jones, J. Am. Chem. Soc. **1982**, *104*, 1316
[17] N.D. Sinha, P. Davis, L.M. Schultze, K. Upadhya, Tetrahedron Lett. **1995**, *36*, 9277
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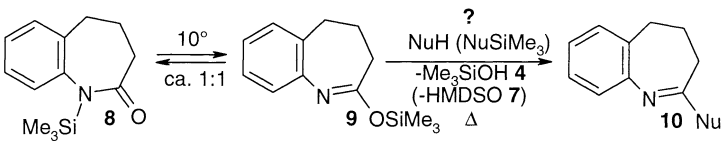
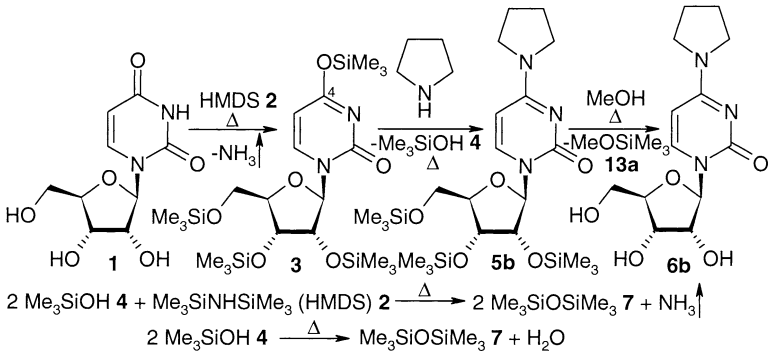


Scheme 1.2

After three previous short reviews [20–22] covering mainly our own work, this review discusses initially, in Chapters 1–3, the techniques of preparative silylation, the properties of the different silyloxy leaving groups, and the techniques of desilylation. The major part of this review, beginning with Chapter 4, however, surveys the different applications of silylation–activation and silicon-induced reactions of a whole range of functional groups in which hydroxy groups are eliminated as silyloxy-leaving groups ranging from trimethylsilanol **4** to hydrated forms of SiO_2 or Cl_3SiOH while these functional groups are transformed into amino-, oxygen-, halogen, or C-substituents; in these chapters we describe our own work as well as that by other groups. Because of the large number of publications, e.g. on reductions with silanes in Section 12.2, this review is not, and cannot be, comprehensive but tries to indicate the most important trends and to quote reviews in each particular field.

1.1 Experimental Example



Scheme 1.3

[20] H. Vorbrüggen, K. Krolikiewicz, U. Niedballa, Ann. N.Y. Acad. Sci. **1975**, *255*, 82
[21] H. Vorbrüggen in "Current Trends in Organic Chemistry", Ed. H. Nozaki, Pergamon Press, Oxford, **1983**, pp. 323–330
[22] H. Vorbrüggen, Acc. Chem. Res. **1995**, *28*, 509

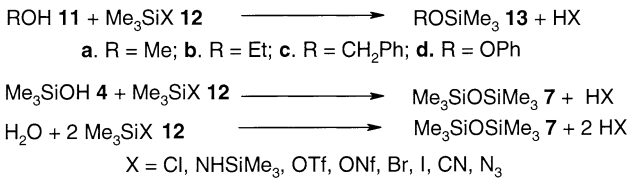
In a 100 mL round-bottomed flask connected to a reflux condenser, 4.88 g (20 mmol) uridine **1** is suspended and stirred in 12.44 mL (60 mmol) HMDS **2**, 4.15 mL (50 mmol) pyrrolidine, 0.1 mL Me_3SiCl **14**, and 15 mL abs. pyridine. After 4.5 h heating in an oil bath at 140–145 °C the reaction mixture turns yellowish and is complete according to TLC (acetone–methanol, 3:1). After evaporation of the solvents *in vacuo*, the yellowish, partly crystalline residue of crude **5b** is boiled for 3 h in 100 mL methanol and then kept at room temperature for 16 h. After evaporation of the solvent, 6.09 g crude 4-pyrrolidino-1-(β-D-ribofuranosyl)-1,2-dihydropyrimidine-2-one **6b** is obtained. This is recrystallized from 90 mL boiling methanol and subsequently from 30 mL methanol to give, in two crops, 5.677 g (95.4%) pure **6b**, m.p. 211–213 °C [11].

2
Techniques for Preparative Silylations–Desilylations

2.1
Silylations with Monofunctional Silylating Reagents

Polar functional groups such as alcohols or phenols **11** or trimethylsilanol **4** are transformed by monofunctional silylating reagents Me_3SiX **12** into their lipophilic and often volatile trimethylsilyl ethers **13** whereas water is converted into persilylated water (= $Me_3SiOSiMe_3$, hexamethyldisiloxane, HMDSO, **7**, b.p. 100 °C). The persilylation of phenols and, in particular, catechol (or hydroquinone) systems (Scheme 2.1) protects them efficiently against air oxidation even at temperatures of up to 180 °C. (cf., e.g., the silylation–amination of purine nucleosides with dopamine hydrochloride in Section 4.2.4)

For preparative purposes the most important and cheapest monofunctional reagents Me_3SiX **12** are trimethylchlorosilane (TCS) **14** (b.p. 57 °C) (**12**, X = Cl) and hexamethyldisilazane (HMDS) **2** = $Me_3SiNHSiMe_3$ (b.p. 126 °C) (**12**, X = $NHSiMe_3$), which are both produced on a large technical scale. Because HCl is formed on silylation of functional groups with TCS **14**, bases such as triethylamine must be added, e.g., on silylation of amino acids or peptides [1, 1a, 1b, 2], preferably in boiling CH_2Cl_2, to give the desired *N,O*-bis(trimethylsilylated) amino acids or dipeptides and the insoluble $Et_3N \cdot HCl$ [2]. The silylation of *a*-amino acids [1] with



Scheme 2.1

[1] L. Birkofer, A. Ritter, Chem. Ber. **1960**, *93*, 424
[1a] K. Rühlmann, Chem. Ber. **1961**, *94*, 1876
[1b] K. Rühlmann, J. Hills, H.-J. Graubaum, J. Prakt. Chem. **1966**, *32*, 37
[2] H.R. Kricheldorf, Liebigs Ann. Chem. **1972**, *763*, 17

boiling HMDS **2** at 130 °C affords the desired *N,O*-bis(trimethylsilylated)amino acids whereas on silylation of 3- or 4-aminocarboxylic acids and dipeptides with boiling HMDS **2** the corresponding pyrrolidones, piperidones, or diketopiperazines [2, 2a] are obtained, as discussed in Section 9.2.

On silylation with HMDS **2** only ammonia is formed, and is normally evolved without participating in the reactions. Exceptions are silylation–aminations of carboxylic acids with HMDS **2** at room temperature to give 80–85% of the desired *O*-trimethylsilyl esters and up to 15% of ammonium carboxylates $RCO_2^-NH_4^+$ [2b]. But, as subsequently shown in Scheme 4.1, the corresponding amides can also be formed. Furthermore, silylation–aminations of heterocyclic lactam systems with HMDS **2** afford, at higher temperatures under pressure, amino-*N*-heterocycles (cf. Sections 4.2.1–4.2.5). HMDS **2** can also add to pyrones in the presence of DBU to give pyridine-2-ones [3] or to 2-(trifluoromethyl)acrylic acid in CH_2Cl_2 to give 2-trifluoro-3-aminopropionic acid [4]. HMDS **2** converts *β*-diketones into pyridines (cf. Section 5.5.1) and 1,4-diones into pyrroles [4a, b] (cf. Section 9.4).

Silylations of alcohols or phenols **11** with HMDS **2** are accelerated by acidic catalysts [5–7] such as small amounts of trimethylchlorosilane (TCS) **14**, whereupon ammonium chloride is generated during silylation. On silylation of alcohols or phenols **9** with equivalent amounts of HMDS **2** and TCS **14** [8] at ambient temperature in absolute acetonitrile the silylated alcohols or phenols **13** are obtained, and an equivalent amount of ammonium chloride, which rapidly precipitates from acetonitrile during the reaction, indicating the progress of silylation [9]. Obviously, the ammonium chloride can be removed by filtration during work-up with exclusion of humidity. Alternatively, on boiling such a reaction mixture in acetonitrile the ammonium chloride sublimes into the reflux condenser and can thus be removed by changing the reflux condenser. Several publications report use of other ratios of HMDS **2** and TCS **14**, from a ratio of two equivalents of HMDS **2** to one equivalent TCS **14** to a ratio of one equivalent of HMDS **2** to two equivalents of TCS **14** [10]. In the latter reaction the generated HCl is only partially neutralized by the liberated ammonia. In the rapid reaction of TCS **14** with small amounts of water in the presence of bases such as triethylamine trimethylsilanol **4** is formed as an intermediate which dimerizes on heating, especially in

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[4] I. Ojima, K. Kato, K. Nakahashi, T. Fuchikami, M. Fujita, J. Org. Chem. **1989**, *54*, 4511
[4a] B. Rigo, D. Valligny, S. Taisne, Synth. Commun. **1988**, *18*, 167
[4b] B. Rousseau, F. Nydegger, A. Gossauer, B. Bennua-Skalmowski, H. Vorbrüggen, Synthesis **1996**, 1336
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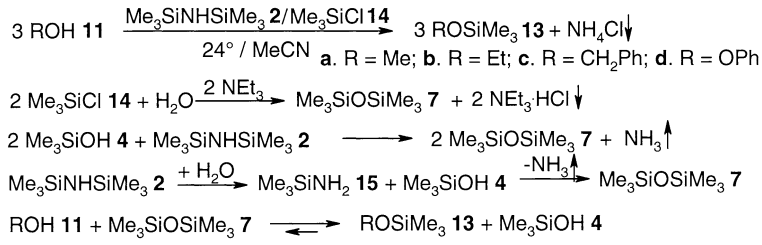

Scheme 2.2

the presence of acidic catalysts, to HMDSO **7** and water (cf. Chapter 3). This water must be removed by additional amounts of TCS **14**/triethylamine, TCS **14**/HMDS **2** or HMDS **2** alone, as depicted in Scheme 2.2. The reaction of two equivalents of trimethylsilanol **4** with HMDS **2** to HMDSO **7** and ammonia has already been mentioned in the Introduction (Chapter 1). Even HMDSO **7**, which is cleaved by alkali hydroxides to the crystalline alkali trimethylsilanolates (cf. Section 3.1), has been used as a mild silylation reagent [11–13] to give, in equilibrium with alcohols ROH **11**, the silylated alcohols **13**. Addition of HMDSO **7** to a radical reaction of lauroyl peroxide with an olefin containing a tertiary alcohol apparently protects the alcohol against dehydration [13]. The slow reaction of HMDS **2** with water affords trimethylsilanol **4** and trimethylsilylamine **15**, which is probably an intermediate in silylations with HMDS **2** but can, however, only be isolated under special reaction conditions [14]. Trimethylsilanol **4** and trimethylsilylamine **15** combine normally on heating to HMDSO **7** and ammonia, which evolves. On preparative silylations, silylation-aminations (cf. Sections 4.2.1–4.2.5) or silylation–C-substitutions (cf. Section 4.8) employing HMDS **2**, the initially generated trimethylsilanol **4** (b.p. 99 °C) and the subsequently formed HMDSO **7** (b.p. 100 °C) give rise to an azeotropic mixture (b.p. 89–91 °C) [15] which, like pure **7**, can be readily removed by distillation over a small distillation column and thus separated from as yet unreacted HMDS **2** (b.p. 126 °C). In the closely related reaction of methoxytrimethylsilane **13a** with trimethylsilanol **4** to give HMDSO **7** and MeOH, HCl as catalyst is 500 times more active than KOH [16].

Further important silylating reagents Me_3SiX **12** are Me_3SiBr **16** [17], Me_3SiI **17** [18, 19] (Scheme 2.3), Me_3SiCN **18** [19, 20a], and Me_3SiN_3 **19** [19, 20], most of

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[16] M. Grubb, J. Am. Chem. Soc. **1954**, *76*, 3408
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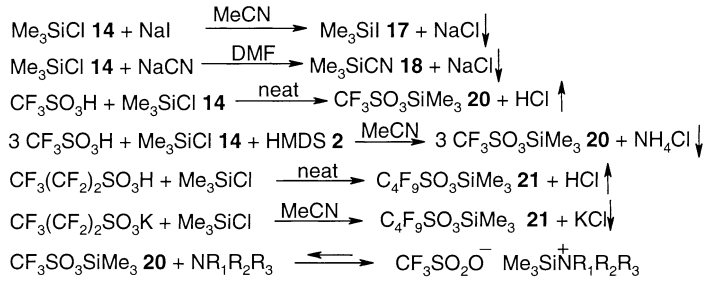

Scheme 2.3

which can be readily prepared *in situ* from TCS **14** in combination with NaI [22, 23] (cf. Section 12.1), NaCN, KCN [19, 24] (cf. Section 7.1), or NaN_3 [19, 20] in acetonitrile or DMF. A very reactive silylating agent is trimethylsilyl triflate $CF_3SO_2OSiMe_3$ (TMSOTf) **20** [25, 25a, 25b, 26], which is prepared on boiling triflic acid with TCS **14**, with evolution of HCl [27], *in situ* from triflic acid and a mixture of TCS **14** and HMDS **2** [28, 29], or, much less economically, on reaction of triflic acid with allyltrimethylsilane **82** [30], tetramethylsilane [31], or 3-trimethylsilyl-2-oxazolidinone [32]. The even more reactive trimethylsilyl nonaflate, *n*-$C_4F_9SO_2OSiMe_3$ (TMSONf) **21**, is synthesized analogously from free nonaflic acid with TCS **14**, with evolution of HCl, or prepared *in situ* from potassium nonaflate and TCS **14** in acetonitrile with formation of KCl [28, 29]. TMSOTf **20** and TMSONf **21** are used in combination with tertiary bases such as triethylamine [33], diisopropylethylamine (DIPEA; Hünig's base) [33, 34], or DBU [35, 36]. Although trimethylsilyl iodide **17** [18, 19] is very reactive in some silylations in the presence of triethylamine, e.g. in the conversion of ketones into their trimethyl-

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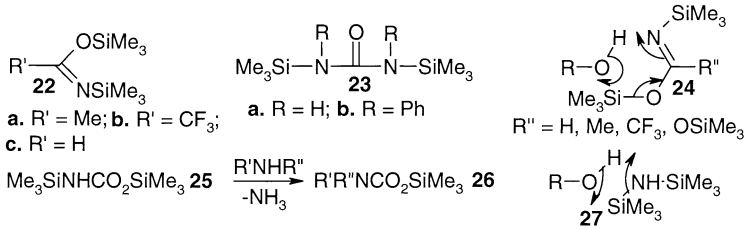
silyl enol ethers [37, 38], **17** can cause a number of side-reactions such as readily cleaving esters and ethers. Trimethylsilyl cyanide **18**, which has the least bulky cyanide as leaving group, has been used successfully for silylation of sterically hindered 2,6-dimethylphenol [20] or tertiary alcohols [20a, 21].

It is obvious that the silylating power of all these silylating agents Me_3SiX depends on the leaving group capability of X. Consequently one can expect the following sequence of the silylating power of Me_3SiX: $X = NHSiMe_3 < Cl < I < OSO_2CF_3 < OSO_2C_4F_9$, although Me_3SiI **17** occasionally seems to be superior to TMSOTf **20** [37, 38]. In particular, the very strong silylating agents TMSOTf **20** or TMSONf **21** can be expected to interact with tertiary bases such as triethylamine or diisopropylethylamine (DIPEA) and with aromatic heterocyclic bases such as pyridine or substituted (*O*-trimethylsilylated) pyridines or pyrimidines to form σ-complexes [38, 38a], whose amounts in the equilibria can be measured by NMR [38, 38a] and which are the active silylating species (c.f. the last reaction in Scheme 2.3).

Alternative silylating reagents such as *N,O*-bis(trimethylsilyl)acetamide **22a** (BSA) [39–43], *N,O*-bis(trimethylsilyl)trifluoracetamide **22b** (BSTFA) [44], or *N,N*-bis(trimethylsilyl)formamide **22c** (BSF) [41, 46], in which the *N*- and *O*-trimethylsilyl groups are in equilibrium [45] (Scheme 2.4), are much more powerful silylating reagents [40, 45] but are more expensive than HMDS **2**, because they are usually prepared by heating formamides or acetamides with TCS **14**/triethylamine



Scheme 2.4

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or with HMDS **2**. They are, furthermore, less practical for preparative silylations, because the liberated free formamides or acetamides usually remain in the reaction mixture and can thus complicate work-up of the reaction mixture and the isolation of the final products. On working, however, with equivalent amounts of BSA **22a**, *N*-trimethylsilylacetamide, which boils at 45–47 °C/0.2 mm [40], is formed and can thus be removed by distillation after silylation of non-volatile end products. These activated *N,O*-bis(trimethylsilylated)amides **22** (cf. also *N,O*-bis(trimethylsilyl)benzamide **296**) or generally **37** (R′ = $Si(Me_3)$ can, however, be expected to react with primary or secondary amines in the presence of, e.g., NH_4Cl or NH_4I, giving the corresponding amidinium salts (Section 4.2.2).

The mono-silylated or free acetamides, which are liberated during silylation with **22a**, can, furthermore, interfere with any subsequent reaction, e.g. with electrophiles. Thus in the one-pot/one-step silylation, Friedel–Crafts catalyzed, nucleoside synthesis starting from protected sugar derivatives and pyrimidine or purine bases, the mono- or bis-silylated amides such as **22a** can compete with less reactive silylated heterocyclic bases for the intermediate electrophilic sugar cation to form protected 1-acetylamino sugars in up to 49% yield [42, 47]. On silylation with trimethylsilylated urea **23a** the liberated free urea is nearly insoluble in most solvents, for example CH_2Cl_2, and thus rapidly precipitated [43].

As already mentioned, the *N,O*-bis(trimethylsilyl)amides **22** (see Scheme 2.4) and *N,N*-bis(trimethylsilyl)ureas such as **23a** and **23b** [48] are much faster silylating reagents than HMDS **2**, because silylation with **22a** is energetically favored by 9 kcal mol^{-1} over silylation with HMDS **2** [49]. Thus the highly hindered 2,6-di(*tert*-butyl)phenol is converted to its trimethylsilyl ether on heating to 90 °C with BSA **22a** in acetonitrile for 15 h whereas Me_3SiCl **14**/NEt_3 gives, after boiling for 5 days, only 10% of the trimethylsilyl ether [40]. The *N,O*-bis-(trimethylsilyl) amides **22** and ureas such as **23a** and **23b** probably also react with alcohols or phenols **11** and with trimethylsilanol **4** *via* a six-membered cyclic transition state **24**. An alternative silylating reagent for preparative applications, which is also commercially available, *N,O*-bis(trimethylsilyl)urethane or *N,O*-bis(trimethylsilyl) carbamate **25** [50] probably silylates similarly *via* a six-membered transition state such as **24** giving, however, only carbon dioxide and ammonia as side products. Yet **25** reacts with primary or secondary amines to give ammonia and trimethylsilyloxyurethanes **26** [51], which afford, e.g., with excess aniline at 185 °C, *N,N′*-diphenylurea and the replaced secondary amine such as diethylamine and HMDSO **7** [51a].

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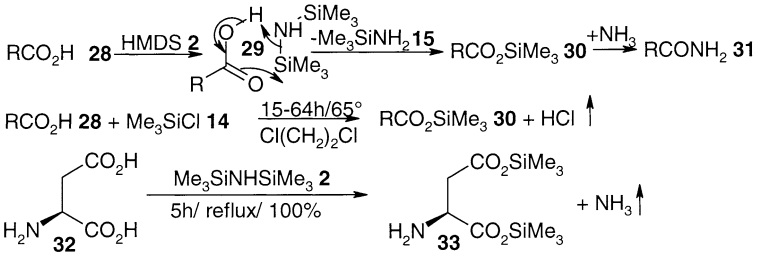
Silylation of alcohols or phenols **11** with HMDS **2** (compared, e.g., with **22**) to their silyl ethers **13** and of trimethylsilanol **4** with HMDS **2** to HMDSO **7** proceeds more slowly, because **2** silylates the alcohols or phenols **11** and **4** apparently *via* an kinetically less favored four-membered cyclic transition state **27** (Scheme 2.4).

Although the rate of silylation of carboxylic acids **28** is generally considered to be lower than the rate of silylation of alcohols and phenols (cf. the subsequently discussed sequence of silylation rates of different functional groups), reactions of carboxylic acids **28** (see Scheme 2.5) with HMDS **2** proceed probably likewise *via* a favorable six-membered transition state such **29** to afford the trimethylsilyl esters **30**, ammonia, and trimethylsilylamine **15**, which converts another equivalent of carboxylic acid **28** into **30**. Carboxylic acids **28**, for example trichloroacetic acid, can also be readily converted into trimethylsilyl ester **30** by heating with TCS **14** in 1,2-dichloroethane at 65 °C with evolution of HCl [52]. Because HMDS **2** is a base, protonation of the nitrogen in the transition state **29** probably proceeds and eases the transfer of the trimethylsilyl group to the carbonyl group. Thus, the two carboxyl groups in L-aspartic acid **32** are readily and selectively silylated on reflux with excess hexamethyldisilazane **2** to afford the bis(trimethylsilyl) ester **33** in quantitative yield, whereas the less reactive amino group will only be silylated on extensive heating with HMDS **2**, as demonstrated in the subsequently described silylation of allylamine **41** to mono(trimethylsilyl)allylamine **42** and bis(trimethylsilyl) allylamine **43** (cf. also the reactivity scale in Scheme 2.7) [53]. *N,O*-Bis(trimethylsilyl)amino acids, which are obtained from amino acids with TCS **14**/triethylamine in benzene, can be readily reduced to aminoalcohols, in high yields, by $LiAlH_4$ in Et_2O [54].

But, as already mentioned, on working at ambient or lower temperatures and normal pressure, and at higher temperatures under pressure, the trimethylsilyl esters **30** react slowly with the liberated ammonia (or trimethylsilylamine **15**) to form the primary amides **31** (Scheme 2.5) or their *N*-monosilylated analogs (cf. Section 4.2.1).



Scheme 2.5

[52] H. H. Hergott, G. Simchen, Synthesis **1980**, 626
[53] A. M. Castaño, A. M. Echivarren, Tetrahedron **1992**, *48*, 3377
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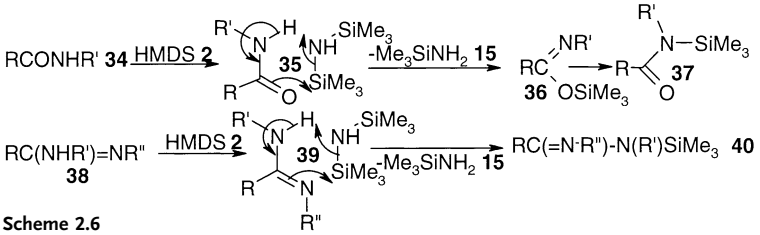
One can also assume that amides, peptides, lactams **34** (Scheme 2.6) and amidines **38** are silylated analogously on heating with HMDS **2**, *via* cyclic six-membered transition states such as **35** and **39**, to their mono(trimethylsilyl)derivatives **36** or **40** (cf. Section 4.2.2). The mono(trimethylsilyl) amides **36**, which rearrange to **37**, and the mono(trimethylsilyl)amidines **40** are converted on longer heating with HMDS **2**, when R′ = H, *via* transition states analogous to **35** (R′ = $SiMe_3$) to bis(trimethylsilyl)amides such as **37** (with R′ = $SiMe_3$ = **22**) or *via* transition state **39** (R = $SiMe_3$) to the bis(trimethylsilyl) amidines **40** (R′ = $Si(Me_3$; see also Section 5.1.3).

In view of the above discussed rapid silylation of hydroxy compounds with silylated amides **22** or ureas **23** compared with silylations with HMDS **2**, small amounts of primary amides such as acetamide, formamide or urea and *N*-phenylurea might act as catalysts to accelerate silylations of alcohols, phenols, or hydroxy *N*-heterocycles with HMDS **2** *via* formation of **22a**, **22c**, or **23**. It is, furthermore, obvious, and has been known for quite a number of years, that addition of protons or Lewis acids to the nitrogen of HMDS **2** [5–8, 55, 56] in four-membered transition states **27** and six-membered transition states **24** will weaken the nitrogen–silicon bond in HMDS **2**, and in other silylating reagents such as **22**, and thus facilitate and accelerate transfer of trimethylsilyl groups in silylations. By several different methods the basicity of nitrogen-containing silylating agents such as hexamethyldisilazane **2** has been estimated to be lower than that of the corresponding substituted amines [55, 56]. Nevertheless, the nitrogen in HMDS **2** is still basic enough to enable activation of the nitrogen by protonation or addition of a Lewis acid [8]. Because alcoholic hydroxyl groups apparently form alcoholates with the strong base DBU, these alcoholates will also attack HMDS **2** to give the corresponding silylated alcohols. It should, furthermore, be noted that different functional groups are silylated with quite different reaction rates by HMDS **2** (or other silylating agents) [5]. Whereas alcohols, phenols, and carboxylic acids are usually silylated most rapidly, amines and, in particular, mercaptans react much more slowly. Mercaptans are usually only silylated under special conditions, because compounds R–S–$SiMe_3$ are less favored combinations between the "hard"



Scheme 2.6

[55] A. W. Jarwie, D. Lewis, J. Chem. Soc. **1963**, 1073

[56] G. Huber, H. Schmidbaur, Z. Naturforsch. **1998**, *53b*, 1103

$ROH \geq ArOH \geq RCOOH \geq RCONH_2 >> R\text{-}NH_2 >> R\text{-}SH$

Scheme 2.7

potential Me_3Si cation and the "soft" mercaptide anion [57, 58] (Scheme 2.7) (cf. also Chapter 8).

Because steric factors strongly influence the rate of silylations, primary alcohols are normally silylated much more rapidly than secondary alcohols whereas tertiary alcohols are silylated much more slowly. The same is true for phenols – ortho-substituted phenols such as *o*-cresol are silylated much more slowly than unsubstituted phenols. Obviously, the same applies to cleavage of silylated alcohols or phenols on transsilylation, e.g. with excess boiling methanol (Section 2.3).

The relatively slow rate of silylation of amines ensures the presence of free amines in silylation–aminations (Sections 4.2.1–4.2.5) and enables selective silylation of alcoholic or phenolic hydroxyl groups or carboxyl groups in mono- or polyhydroxy amines or amino acids (cf. also the ready formation of **33**). This order of reactivity reflects the thermodynamic stability of *O*-trimethylsilyl derivatives, because the *O*-trimethylsilyl bond in trimethylsilylated alcohols and phenols **11** is much stronger than, e.g., a nitrogen-silicon bond as in silylated amines, which are silylating agents. Typically, primary amines such as allylamine **41** (Scheme 2.8) are only silylated to mono-silylated allylamine **42** on heating for 18 h with HMDS **2**/$(NH_4)_2SO_4$ [59, 59a] or with HMDS **2**/TCS **14** [59b]. Allylamine **41** (and other primary amines) can, however, be silylated with TCS **14** in the presence of triethylamine and $TiCl_4$ in 83% yield to the persilylated allylamine **43** (or to other *N,N*-bis(trimethylsilyl)-amines) [60]. Additional methods for preparation of *N,N*-bis(trimethylsilyl) primary amines such as benzylamine, aniline, or alanine employing trimethylsilyl triflate **20** or Me_3SiI **17** in combination with triethylamine without solvent or in boiling 1,2-dimethoxyethane have recently been summarized [60]. Persilylated amines such as **43** or the more stable stabase derivatives **46**, which are obtained from primary amines **44** on treatment with the bifunctional silylating agent 1,2-bis(chlorodimethylsilyl)ethane **45** [44, 61], are not affected by quite a range of organometallic reagents [61, 62]. On treatment with aqueous acids the amine **44** is recovered and the bis(sila)hydrofuran **47** is obtained; this compound is also commercially available.

For silylation of mercapto groups or hindered amide systems, the combination of HMDS **2** with TCS **14** [8] (cf. also Section 5.1.5), or the combination of tri-

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[59] J. L. Speier, R. Zimmerman, J. Webster, J. Am. Chem. Soc. **1956**, *78*, 2278
[59a] J. Hils, V. Hagen, H. Ludwig, K. Rühlmann, Chem. Ber. **1966**, *99*, 776
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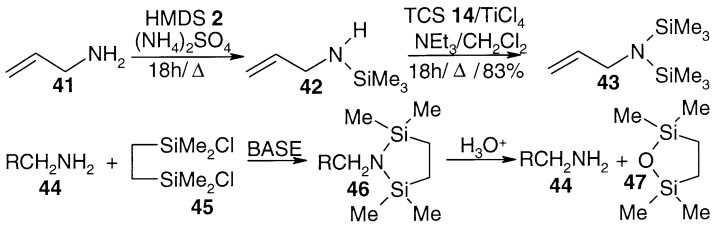

Scheme 2.8

methylsilyl triflate **20**, trimethylsilyl nonaflate **21**, or trimethylsilyl cyanide **17** with triethylamine or a strong base such as DBU (cf. cyclizations in Chapter 9) or reaction of the lithium salts of mercaptans with TCS **14** or trimethylsilyl triflate **20** should always be regarded as a last resort.

Whereas silylations with trimethylchlorosilane (TCS) **14** (b.p. 57 °C) demand the presence of a base to neutralize the HCl evolved, giving rise to the hydrochloride of the base, the use of hexamethyldisilazane (HMDS) **2** (b.p. 126 °C), in particular in the presence of 0.01–0.05 equivalents of acidic catalysts such as TCS **14** or ammonium sulfate, should **normally** be preferred as the preparative silylating reagent, because HMDS **2**:

- gives, on silylation, only volatile ammonia as a side product and traces of ammonium chloride if small amounts of TCS **14** are used as a catalyst, and
- enables silylations at normal pressure at temperatures of up to ca. 130 °C.

Last but not least HMDS **2** is, in the laboratory and in pilot plants, quite stable when stored in a normal closed vessel whereas trimethylchlorosilane (TCS) **14** should be stored in a hood, because it reacts with humidity to hexamethyldisiloxane **7** and HCl. Because HMDS **2** is a very non-polar compound, the silylation of very polar compounds, e.g. purines or pteridines, with HMDS **2** will often proceed only on addition of a polar solvent such as pyridine which is, however, readily removed after silylation, with excess HMDS **2**, on codistillation with abs. xylene. Interestingly, it was recently reported that addition of catalytic amounts of iodine dramatically accelerates the silylation of alcohols, in particular tertiary alcohols, with HMDS **2** in CH_2Cl_2 at room temperature [63].

It should be noted here that the lithium salt of hexamethyldisilazane Li-HMDS **492** (and Na-HMDS-(**486**) and K-HMDS in Sections 5.1.2 and 5.1.3), which is readily obtained on treatment of a solution of HMDS **2** in hexane or THF with butyllithium at –78 °C, is not only a very useful and selective strong base, e.g. for Wittig reactions, but can also add to carbonyl groups to yield the silylated Schiff bases or nitriles (cf. Sections 4.7 and 5.1.3) or to nitriles to afford *N*-silylated amidines. Alkylation of the Li-HMDS **492**, e.g. with allyl bromide, affords, furthermore, *N*,*N*-bis(trimethylsilylated) primary amines such as **43** [64]. The combina-

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