This article is published as part of the Dalton Transactions themed issue entitled:

New Horizon of Organosilicon Chemistry

Guest Editor: Professor Mitsuo Kira Tohoku University, Japan

Published in issue 39, 2010 of Dalton Transactions



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Unsuccessful attempts to add alcohols to transient 2-amino-2-siloxy-silenes leading to a new benign route for base-free alcohol protection[†]

Tamaz Guliashvili,^{*a,b*} Julius Tibbelin,^{*a*} Jiyeon Ryu^{*a*} and Henrik Ottosson^{*a*}

Received 17th April 2010, Accepted 6th July 2010 DOI: 10.1039/c0dt00323a

Thermolytic formation of transient 1,1-bis(trimethylsilyl)-2-dimethylamino-2-trimethylsiloxysilene (2) from N,N-dimethyl(tris(trimethylsilyl)silyl)methaneamide (1) in presence of a series of alcohols was investigated. The products are, however, not the expected alcohol-silene addition adducts but silylethers formed in nearly quantitative yields. Thermolysis of 1 in the presence of both alcohols (MeOH or iPrOH) and 1,3-dienes (1,3-butadiene or 2,3-dimethyl-1,3-butadiene) gives alkyl-tris(trimethylsilyl)silvlethers and the [4+2] cycloadducts between the silene and diene, which confirms the presence of 2 and that it is unreactive towards alcohols. The observed silvlethers are substitution adducts where the amide group of the silylamide is replaced by an alkoxy group, and the reaction time is reflected in the steric bulk of the alcohol. Indeed, the formation of silvlethers from the reaction of alcohols with silylamide represents a new base-free method for protection of alcohols. The protection reactions using 1 progresses at elevated temperatures, or alternatively, under acid catalysis at ambient temperature, and similar protections can be carried out with N-cyclohexyl(triphenylsilyl)methaneamide and N,N-dimethyl(trimethylsilyl)methaneamide. The latter silylamide can be used under neutral conditions at room temperature. The only by-products are formamides (N,N-dimethylformamide (DMF)) or *N*-cyclohexylformamide), and the reactions can be performed without solvent. In addition to alcohols we also examined the method for protection of diols, thiols and carboxylic acids, and also these reactions proceeded in high yields and with good selectivities.

Introduction

Compounds with Si=C double bonds, so-called silenes,¹ are highly air and moisture sensitive and this hampers the facile application of reactions involving these compounds in target directed synthesis. Often the regiochemistry of water and alcohol additions is strongly in favor of the Si–O bonded adducts,² and Veszprémi, Kira and co-workers verified through quantum chemical calculations that water addition to the Si of the parent silene is a strongly exothermic process that proceeds with a low activation energy.³ The addition of the O atom to the C end, on the other hand, was calculated to pass over a prohibitively high barrier for the reaction to proceed at ambient temperature.

Whereas the parent silene readily adds water to the Si end it has been concluded that reducing the Si^{$\delta+$}==C^{$\delta-$} bond polarity is one possible means to temper the reactivity of silenes.^{4,5} This reduction of the Si=C bond polarity can be effected through the reversepolarized resonance structures **II** and **III** of Scheme 1, and the isolable silene with X = OSiMe₃ and Y = 1-Ad formed by Brook and co-workers in 1981 is a first example of such a silene.⁶ The importance of reversed Si=C bond polarization for the kinetic stabilization of silenes was highlighted by Apeloig and co-workers as they showed through computations that the activation energy needed for water addition across the Si=C bond, leading to the





Si–O bonded adduct, increases gradually with the influence of reversed polarization.⁷ Silenes influenced by reversed Si^{δ}==C^{δ +} polarization should therefore be less sensitive to moisture than naturally Si^{δ +}==C^{δ -} polarized silenes, possibly facilitating their formation and handling by conventional synthetic techniques. Indeed, Leigh and co-workers have verified in a series of studies on transient silenes formed through laser flash photolysis that their reactions with methanol markedly depends on the polarity of the Si=C bond.⁸ Whereas π -donor/ σ -acceptor substituents at Si increase the electrophilicity of the Si=C bond, π -acceptor/ σ -donor substituents at Si and π -donor substituents at C have the opposite effect.

Noteworthy, in all systems examined by Leigh and co-workers the regiochemistry was in accord with the addition of the alkoxy moiety to Si. Yet, it has been observed in two other cases that water and alcohol additions to silenes can proceed with opposite regiochemistry to the normal, yielding C–O instead of Si–O bonded adducts.^{9,10} These findings were reported by Kira and coworkers for the addition of methanol to a 4-silatriafulvene,⁹ and by the group of Sekiguchi for water addition to a 1-silaallene.¹⁰ A common feature of the 4-silatriafulvenes and 1-silallenes is that they are influenced by reversed Si=C bond polarization,^{11,12}

^aDepartment of Biochemistry and Organic Chemistry, Uppsala University, Box 576, 751 23, Uppsala, Sweden. E-mail: henrik.ottosson@kemi.uu.se; Fax: +46 (0)18 471 3818; Tel: +46 (0)18 471 3809

^bGE Power and Water, Water & Process Technologies, 4636 Somerton Road, Trevose, PA, 19053, USA

[†] Electronic supplementary information (ESI) available: Additional experimental details. See DOI: 10.1039/c0dt00323a

but this influence is moderate as their Si atoms have planar or nearly planar configurations and their Si=C bond lengths, measured as 1.704–1.755 Å, are closer to those of normal Si=C double bonds than normal Si-C single bonds (~1.70 and ~1.87 Å, respectively).^{13,14} This is in contrast to a silene which is strongly influenced by the reverse polarized resonance structures **II** and **III** because this species will be Si-C single rather than Si=C double bonded and its Si should be markedly pyramidal.⁵ Silenolates are closely related to such strongly reverse polarized silenes as their negative charge is predominantly localized to the Si atom,^{5,15} verified through our crystal structure of [18]crown-6 potassium 1,1-*bis*(trimethyl)silyl-2-*tert*-butylsilen-2-olate.¹⁶

Earlier, we formed the transient 1,1-*bis*(trimethylsilyl)-2dimethylamino-2-trimethylsiloxysilene (**2**, Scheme 2) through thermolysis of *tris*(trimethylsilyl)silyl-*N*,*N*-dimethylamide (**1**).¹⁷ Quantum chemical B3LYP/6-31G(d) calculations indicated that this silene is dominated by resonance structures **II** and **III** as it has an Si–C bond length of 1.870 Å and a pyramidal Si with $\Sigma \alpha$ (Si) of 336.6°. Hence, **2** is a suitable species for studying the reactivity of a silene strongly influenced by reversed SiC bond polarity toward alcohols. At this point it should be noted that strongly reversepolarized silenes formed through [1,3]-silyl shifts from suitable acylsilane precursors will likely only be transient species as the barrier for the back-transfer of the TMS group will be low as a result of the strong single bond character of the formal Si=C double bond.¹⁸



Whereas applications of unsaturated Si compounds in targetdirected synthesis is an emerging research area of current organosilicon chemistry,¹⁹ the applications of various silyl reagents for protection of alcohols, thiols, and carboxylic acids is presumably the most well-explored and mature topic within the field.^{20,21} As will be shown, the results given herein can, however, also expand this last field by providing a benign and base-free alcohol protection protocol.

The most common protection methods use trialkylsilyl halides or triflates,¹⁹⁻²² and reactions with these reagents are generally base-promoted or sometimes catalysed by, *e.g.*, magnesium or lithium sulfide. A range of other silyl reagents exist,²³⁻³² but nearly all of these reagents require a catalyst, or they need to be carried out in solvent, and/or the reactions give byproducts that are not easily removed. An early example of a more benign method is Kuwajima's nearly solvent-free method for alcohol and ketone protection using ethyl trimethylsilylacetate (ETSA) with tetrabutylammonium-fluoride (TBAF) as catalyst.³³ More recently, the base and catalyst free silylation using silyl methallylsulfinates, described by Vogel,³⁴ is promising, however, gives sulfur dioxide as a by-product.

Herein, we report on studies of the fundamental reactivity of a strongly reverse-polarized silene in comparison with the reactivities of naturally polarized silenes. A spin-off finding from our observations is that the unexpected reactions likely can be exploited in synthesis in a wider sense.

Experimental

The starting materials for the silylamides and the alcohols, thiols, diols, and carboxylic acids used in the study were commercially available, as were the solvents used. All chemicals were used as purchased except THF and toluene which were dried over sodium with sodium benzophenone ketyl as indicator, and CH_2Cl_2 which was dried over calcium chloride. All reactions were performed under inert atmosphere (argon). All purified compounds below were purified on preparative TLC plates or by silica column chromatography, depending on the amount of product (eluent: pentane–EtOAc (98 : 2)), if nothing else noted.

The (thermolytic) reactions of silylamides with alcohols, thiols, diols and carboxylic acids (substrates) were performed according to either of nine different reaction protocols listed below. Further details of the protocols are given in the supporting information. In all protection reactions similar amounts of formamides and protected substrates were formed according to ¹H NMR spectroscopy.

Protocol 1: One equivalent of N,N-dimethyl(*tris*(trimethylsilyl)silyl)methaneamide (1) and four equivalents of alcohol were placed in a dry NMR tube and dissolved in toluene- d_8 . The NMR tube was sealed and placed in an oil bath and heated to 120 °C. The complete consumption of 1 was monitored by ¹H NMR spectroscopy.

Protocol 2: The same reaction procedure as in protocol 1 was also performed at 180 °C.

Protocol 3: The same reaction and amounts as in protocol 1, with one drop of triflic acid added. The reaction started immediately at ambient temperature.

Protocol 4: The same reaction as protocol 3, with the difference that one drop Hünig's base (iPr_2EtN) was used instead of acid. Higher temperature (120 °C) was needed to initiate the reaction.

Protocol 5: One equivalent of alcohol and 1.3 equivalents of silylamide 1 were placed in sealed tubes containing toluene, and the reactions were run at 180 °C. The fastest protections (< 7.5 h) were also performed in refluxing toluene for one night, with yields similar as when run in sealed tubes.

Protocol 6: Same conditions as in protocol 5, except that a temperature of 240 °C was used instead of 180 °C.

Protocol 7: Monofunctionalized substrates were protected at ambient temperature with 1.3 equivalent of N,N-dimethyl-(trimethylsilyl)methaneamide (10), whereas difunctionalized subtrates were protected with 1.1 equivalents of 10. The reactions were performed in sealed NMR-tubes at ambient temperature in CH₂Cl₂ and with a few drops of CDCl₃ added. The protected substrates were not purified due to the poor stability towards aqueous and silica conditions of a few of them. A few also possess low boiling points. Moreover, a limited selection of the reactions were performed neat, and in other solvents such as THF, pentane, toluene and diethyl ether with similar reaction times and conversions as reported for the reactions in CH₂Cl₂.

Protocol 8: The same reaction and reaction conditions as in protocol 7, with DMF instead of CH_2Cl_2 as solvent.

Protocol 9: Protection with the triphenylsilyl group. *N*-cyclohexyl(triphenylsilyl)methaneamide (11) was applied in 1.3 times excess over the substrates, and the reactions were run in toluene in 1.5 ml sealed tubes at $180 \,^{\circ}$ C.

Results and discussion

transient 1,1-bis(trimethylsilyl)-2-dimethylamino-2-tri-The methylsiloxysilene (2, Scheme 2) was formed thermally from N,N-dimethyl-tris(trimethylsilyl)silylmethaneamide (1)by heating at either 120 or 180 °C. Formation of the silene at the higher temperature was previously verified through trapping with 2,3-dimethyl-1,3-butadiene giving the silacyclohexene 4 through a [4+2] cycloaddition reaction between the silene and 1,3-diene followed by a permutation of the substituents of the initial [4+2] cycloadduct 3 (Scheme 2).^{17,35} We could now prove formation of 2 also at the lower temperature as the silene was trapped with 1,3-butadiene, a diene which is more reactive in the [4+2] cycloadditions with 2-amino-2-siloxy-silenes than 2,3dimethyl-1,3-butadiene, thus indicating that the reactions follow the reactivity pattern of inverse-electron-demand Diels-Alder reactions.38

Since silene 2 is formed at both temperatures we first carried out the attempted alcohol-silene reactions at 120 °C as this should lead to less by-products. The reactions were carried out in toluene solutions in sealed tubes containing 1 and either methanol (a), ethanol (b), *iso*-propyl alcohol (c), *tert*-butyl alcohol (d), phenol (e), allyl (f) or benzyl alcohol (g). The ratio of the silylamide to alcohol was set at 1:4, and the progress of the reactions was monitored by ¹H and ¹³C NMR spectroscopy. As seen in Table 1, the reactions with all alcohols except *t*BuOH and phenol were clean yielding only single products in yields that are nearly quantitative. However, the reaction times vary significantly and correlate with the steric bulk of the alcohol.

The identities of the reaction products were next to be determined, and surprisingly these do not correspond to the expected adducts 6 and/or 7 resulting from trapping of the silene by the alcohols. Instead, the major products are in all cases, silvlethers 5 resulting from replacement of the amide group in 1 by the alkoxy group of the alcohol (Scheme 3). The yields of the silylethers reported in Table 1 were determined both from ¹H NMR spectra of the sealed NMR tubes as well as on the isolated compounds. Apart from silvlethers, formation of N,N-dimethylformamide (DMF) in very similar yields to the silvlethers was also observed. With regard to tBuOH, this alcohol reacted considerably slower than the others. In contrast, phenol is the alcohol which is most rapidly consumed, but its yield for the silylether formation is lower than for the aliphatic alcohols. The side-products could not be fully characterized, but could result from trapping of silene 2 by phenol yielding 6 and/or 7. Here, it should be noted that phenol which

Table 1 Reactions of alcohols with N,N-dimethyl(*tris*(trimethylsilyl)-silyl)methaneamide $(1)^a$

ROH	$T/^{\circ}\mathrm{C}$	Time/h	Yield ^b (%) NMR/isolated
MeOH (a)	120	4	96/92
MeOH (a)	180	0.5	95/92
EtOH (b)	120	8	94/90
EtOH (b)	180	0.8	93/89
<i>i</i> PrOH (c)	120	11	93/87
<i>i</i> PrOH (c)	180	1.1	92/85
tBuOH (d)	180	352	—/18
PhOH (e)	120	1.1	—/40
PhOH (e)	180	0.5	—/60
BnOH (f)	120	1	76/68
BnOH (f)	180	0.25	89/84
AllylOH (g)	120	1	70/63
AllylOH(g)	180	0.25	85/78

^{*a*} Conditions: Sealed NMR tubes, toluene-d₈, [silylamide]:[ROH] = 1:4 (protocol 1 (120 °C) and protocol 2 (180 °C)). ^{*b*} Conversions determined by ¹H NMR spectroscopic measurements on sealed NMR tubes, and yield after purification by preparative TLC.



Scheme 3

reacts the fastest also is more acidic than the aliphatic alcohols, a factor that influences the reaction rate (*vide infra*).

In order to probe if silene **2** is formed at all during the thermolysis of **1** when alcohols are present we carried out thermolysis run in precence of both *i*PrOH and 2,3-dimethyl-1,3-butadiene in a 1.1:10 ratio. Indeed, both *iso*-propyl-*tris*(trimethylsilyl)silylether and the [4+2] cycloadduct between silene and diene could be observed in yields of 66 and 27%, respectively. No other side-products were observed, and it can thus be concluded that the silene is present but that the activation energies for the two possible *i*PrOH additions to the silene, yielding **6** and **7**, are so high that these reactions do not occur. Instead, the silene reacts with the diene and the silylamide reacts with *i*PrOH (giving **5**). A similar

Downloaded by FORDHAM UNIVERSITY on 10 December 2012 Published on 24 August 2010 on http://pubs.rsc.org | doi:10.1039/C0DT00323A experiment in presence of both methanol and 1,3-butadiene was also performed, giving both silylether and [4+2] cycloadduct.

To our knowledge the formation of silvlethers 5 instead of the silene trapping adducts 6 and 7 represents the first example where a silene is formed which does not react with an alcohol. The reduced reactivity of silene 2 towards alcohols is in line with previous experimental observations of Leigh and co-workers that the rate of methanol addition to silenes decreases gradually with increased π -donor ability of the substituents at the C terminus. The finding also agrees with the conclusions of Apeloig and co-workers that the activation energy for water addition to silenes is strongly influenced by the degree of reversed Si=C bond polarity since it becomes successively higher when resonance structures II and III increase in importance.⁷ Clearly, in the transient silene 2 the extent of reversed Si=C bond polarization has reached a point where the rate for alcohol addition is so slow that it cannot compete with the reaction of the silylamide in which the C(=O)NMe₂ moiety of 1 is replaced by a methoxy group.

Realizing the poor leaving group ability of the amide group the substitution reaction is most likely not a regular nucleophilic substitution reaction but a process that proceeds by a more complex mechanism, presumably coupled with initial protonation of **1**. Indeed, it is likely that protonation of **1** is the rate limiting step because the reaction rate is increased very significantly when triflic acid is added to a toluene solution of **1** and MeOH in 1:4:0.001 ratio of **1**, MeOH and acid. Interestingly, this reaction ran at room temperature and was completed within 30 min to give the silylether in equally high yield as when run without acid at high temperature. However, the reaction without acid needs 4h at 120 °C for completion. As can be expected, addition of base (*i*Pr₂EtN) to the reaction of **1** with MeOH lead to a reduced reaction rate, supporting that protonation of **1** is an important step in the mechanism.

An in-depth analysis of the mechanism is outside the scope of the present report, and results from computational studies will be given in due course. However, based on the earlier finding of Apeloig and co-workers in a gradual increase in the activation energies for ROH addition as the silenes become gradually more reverse polarized,⁷ it can easily be realized that the barrier for ROH addition to the 2-amino-2-siloxysilenes will be very high, so high that other reactions occur instead. At this point, it should be remarked that Leigh et al. recently showed that the addition of MeOH to three different 1.1-disilvisilenes proceed via methanol dimers rather than via monomers.36 Still, strongly reverse polarized silenes such as 2-amino-2-siloxysilenes do not exhibit the marked electrophilic character of naturally polarized silenes. This implies a low moisture sensitivity in line with our earlier observation that the transient 1,1-bis(trimethyl-silyl)-2-N,N-diphenylamino-2-tri-methylsiloxysilene (9) can be formed and trapped with 2,3dimethyl-1,3-butadiene through reflux in non-distilled (wet) THF giving the corresponding silacyclo-hexene (cf. 4, Scheme 2) in the same high yield as when run in dry toluene in a sealed tube with inert atmosphere.17

However, with regard to silene 9 we previously found its NPh₂ group to be rotated partially out of conjugation with the Si=C double bond so that this silene is less influenced by reversed Si=C bond polarity than $2.^{37}$ It should therefore have a more electrophilic Si. Of this reason, one could expect that thermolytic formation of 9 from *N*,*N*-diphenyl(*tris*(trimethyl-

silyl)silyl)methaneamide (8) in presence of alcohols can yield also the silene-alcohol adducts in addition to the silylethers. Indeed, when carrying out the thermolysis of 8 at 120 °C together with methanol at a silylamide to alcohol ratio of 1:4, the formation of the silvlether was not observed at all. However, the reaction mixture was too complex to separate, possibly a result of degradation of silene-alcohol adducts, compounds that are heavily substituted and that therefore could be prone to rearrange and/or decompose. Interestingly, when 2,3-dimethyl-1,3-butadiene is also included so that the ratio between the silylamide, methanol, and diene is 1:2:2, then the [4+2] cycloadduct is exclusively formed. Clearly, the reaction between the silene and the diene is more rapid than the reaction between the silene and methanol. This finding is in line with our earlier observation that silene 9 could be formed and trapped with 2,3-dimethylbutadiene to the cycloadduct under moist conditions.17

The silvlethers 5 formed through reaction between 1 and various alcohols are also interesting in their own respect as the tris(trimethylsilyl)silyl group, the sisyl group, has been shown by Brook and co-workers to be a protecting group of primary and secondary alcohols which is resistant towards fluoride deprotecting reagents such as KF in 18-crown-6 and CsF.38,39 However, the TMS₃Si group is easily removed photolytically ($\lambda = 254$ nm), giving it an orthogonal reactivity to other silyl groups. Thus, our unsuccessful attempts to add ROH to the transient and strongly reverse polarized 2-amino-2-siloxysilene 2, formed thermally from silylamides, instead represent a new protocol for protecting alcohols with a synthetically interesting silvl group. However, when we examined the reactivity of the transient silene toward ROH we carried out these reactions in fourfold excess of alcohol when compared to silvlamide, whereas for the subsequent alcohol protections we used the silylamide in slight excess. For the monofunctional substrates (alcohols, thiols, and carboxylic acid) we used a 1.3:1 ratio of silylamide vs. substrate, whereas for the difunctional substrates we used a ratio of 1.1:1. In addition to the alcohols of Table 1 we also included octanol (h) and 1methylcyclohexanol (i), as well as isovaleric acid as a carboxylic acid (i) (Table 2).

As shown in Table 2, the reactions all proceed in reasonable times, and in all cases the conversions were relatively consistent on scales ranging from 20 to 500 mg. A potential

Table 2 Protection of various alcohols and isovaleric acid using N,N-dimethyl(*tris*(trimethylsilyl)silyl)methaneamide (1)^{*a*}

Substrate	Time/h	Yield (%)
MeOH (a)	2	93
EtOH (b)	6	96
<i>i</i> PrOH (c)	27	89^{c}
tBuOH (d)	0.17^{b}	96 ^{b,c}
PhOH (e)	$3, 0.17^{b}$	$73, 94^{b}$
AllylOH (f)	4	93 ^c
BnOH (g)	4	91 ^c
Octanol (h)	7	91 ^c
1-Methylcyclohexanol (i)	0.17^{b}	92 ^b
Isovaleric acid (j)	2	95 ^c

^{*a*} Conditions: Sealed NMR tubes, toluene-d₈, [silylamide]:[ROH] = 1.3:1.0 run at 180 °C (protocol 5). ^{*b*} Microwave irradiated to 240 °C (protocol 6). ^{*c*} Conversion determined through ¹H NMR spectroscopic measurements on sealed NMR tubes.

Table 3 Conversions and reaction times for protections of different substrates using 10 in CH_2Cl_2 or DMF at ambient temperature

Substrate	CH ₂ Cl ₂ Con./Sel. (%) ^b	Time/h	DMF ^a Con./Sel. (%) ^b	Time/h
<i>i</i> PrOH (c)	94/	25	96/—	28
tBuOH (d)	97/—	48	92/—	49
PhOH (e)	99/—	30	81/	33
AllylOH (f)	90/	15	86/—	19
BnOH (g)	97/—	13	91/	16
Octanol (h)	87/—	18	88/	15
1-Methylcyclohexanol (i)	96/—	53	86/—	56
Isovaleric acid (j)	87/—	6	91/	9
<i>n</i> BuSH (k)	84/	40	82/—	42
PhCHOHCH ₂ OH ^e (I)	96/85	27	91/82	17
$4-\text{HOC}_6\text{H}_4\text{CH}_2\text{OH}^c$ (m)	95/82	15	94/82	16
HOCH ₂ CH ₂ OH ^c (n)	86/83	28	83/78	28
$HSCH_2CH_2OH^c$ (0)	93/83	20	87/76	19

^{*a*} A small amount of CDCl₃ was added to each sample, to allow the reaction to be followed by NMR. ^{*b*} Monofunctional substrate run at [substrate]:[10] = 1 : 1.3, and difunctional substrates run at [substrate]:[10] = 1 : 1.1 (protocols 7 and 8). ^{*c*} In all cases main selectivity for primary alcohol.

Table 4Protection of alcohols using N-cyclohexyl(triphenylsilyl)-methaneamide (11) at 180 $^{\circ}C^{a}$

ROH	Time/h	Yield (%)
MeOH (a)	1	94
EtOH (b)	1.5	93
<i>i</i> PrOH (c)	2.5	88
PhOH (e)	2.5	85
AllvlOH (f)	1.75	90
BnOH (g)	1.75	87
Octanol (h)	2	93

" Conditions: Sealed NMR tubes, toluene- d_8 , [silylamide]:[ROH] = 1.3 : 1.0 run at 180 °C (protocol 9).

drawback is the elevated temperatures that are needed, but the procedure avoids base which is normally required for alcohol protection using silylchlorides or silyltriflates.⁴⁰ Alternatively, and as shown above for the protection of MeOH, the reactions can be run at room temperature using acid catalysis. Indeed, the protection of *t*BuOH with 1 can be facilitated by acid as the reaction between 1, *t*BuOH, and triflic acid in a ratio of 1:4:0.001 ran to completion in 33 h at room temperature giving a 56% yield.

Noteworthy, when run at neutral conditions at 180 °C the yields for silylether formation are slightly higher than observed previously (73-97%),³⁸ although the earlier studies were carried out at room temperature. With regard to the phenol and tertiary alcohol protections by **1** under neutral conditions, excellent yields are obtained after 10 min of microwave heating at 240 °C in toluene. Finally, yields similar to those above are also obtained for the protection of primary alcohols, phenols and carboxylic acids by **1** when refluxed in toluene for one day.

Although the *tris*(trimethylsilyl)silyl group has interesting features, the regular protecting groups are the trialkylsilyl groups. To explore if our findings of a base-free protocol for protection of alcohols can be expanded also to these groups we tested the use of trimethylsilyl-N,N-dimethylamide **10** and triphenylsilyl-N-cyclohexylamide **11** (Scheme 4).^{41,42} For **10** we expanded the substrates examined so that we tested protection of alcohols, diols, thiols and carboxylic acids (Table 3), whereas for **11** we used a more limited selection (Table 4).



RXH, X = O, S; alcohol, thiol, carboxylic acid 1 / 5: R' = SiMe₃, R' = R''' = Me 10 / 12: R' = R'' = R''' = Me 11 / 13: R' = Ph, R'' = *c*-Hex, R''' = H

Scheme 4 Protection of alcohols, thiols, and carboxylic acids using three different silylamides.

The protections of the alcohols, phenols, carboxylic acids, and thiols with **10** were all performed at room temperature giving good to excellent conversions (Table 3). Isovaleric acid reacted fastest of the thirteen substrates (6-9 h), in line with the observation presented above that acid catalyzes the reaction. While the tertiary alcohols reacted slowest (48–56 h), their conversions remained very high.

With regard to the protection of the two diols, 1-phenylethane-1,2-diol and 4-(hydroxymethyl)phenol, high conversions and good selectivities were achieved with preferred protection of the primary alcohol. Protection of 1-phenyl-ethane-1,2-diol in CH₂Cl₂ gave good conversion and selectivity for the primary alcohol (96 and 85%, respectively). The result was similar for the trimethyl-silylation of 4-(hydroxymethyl)phenol. The protection of the two difunctionalised compounds, hydroxy acetic acid and 2-mercaptoethanol gave mainly protection of the alcohol moiety in high yields. The protection of hydroxy acetic acid proceeds *via* the silylester (kinetic product), which rearrange to the protected alcohol (thermodynamic product), according to ¹H NMR.

The reactions listed in Table 3 were performed in dry CH_2CI_2 or DMF. A few of the substrates were also protected in other dry solvents such as THF, toluene, acetonitrile and chloroform, as well as neat, with similar conversions. As seen in Table 3 a slight decrease in yield is found when changing solvent from CH_2CI_2 to DMF. The only by-product is DMF, *i.e.*, the solvent when the reaction is performed in this medium.

Reaction with silylamide 11, having a bulky Ph₃Si group, was performed in sealed NMR or microwave tubes at elevated

temperatures above 100 °C (Table 4).† Higher temperatures are required in order to achieve good conversions within reasonable time as the $t_{1/2}$ of **11** (~24 h) sets a limit for the reaction time. We carried out the reactions with **11** at 180 °C to achieve reasonable timings for most of the alcohols in the study. Reactions with **11** give *N*-cyclohexylformamide which is also easy to remove by water extraction, preparative TLC, or silica gel chromatography.

There are some general trends for the three silylamides used here. First, the yields of the protected alcohols at the given temperatures are similar for the different silylamides independent of substrate. Secondly, the trends in the relative reaction rates of the protection reactions are similar for the three silylamides at given conditions (room temperature for 10 and 180 °C for 11 and 1) and generally follow the order: carboxylic acid > BnOH ~ allylOH > primary alcohol > secondary alcohol > PhOH > thiol > tertiary alcohol. However, for 1 the rate for protection of the secondary alcohol is substantially slower than that of phenol.

As noted above, we do not yet have a full view of the mechanism of these reactions, although protonation is clearly a key step in the process. At a first glance, there are similarities to the Si–(C=O) bond cleavage of *N*-methyl-*N*-2,6-dimethylphenyltriethylsilylamide reported by Murai *et al.*, however, this process is base promoted.⁴³ The same applies to the finding of Brook and Gilman from 1955 on the reaction of triphenylsilanecarboxylate with catalytic amounts of sodium methoxide or ethoxide in the respective alcohol which gives the corresponding alkoxytriphenylsilane in good yields besides carbon monoxide and sodium methoxide (Scheme 5).⁴⁴ However, both these procedures require the use of a base, whereas our process is catalyzed by acid, indicating distinctly different mechanisms.

$$RO^{-} +$$
 Ph_3Si OMe $ROSiPh_3 + CO + MeO^{-}$

R = H (98%), Me (82%), Et (73%)

Scheme 5 The study by Brook and Gilman of reactions of triphenyl-silanecarboxylate with sodium alkoxides.⁴⁴ Yields in parentheses.

Conclusions

The transient 1,1-*bis*(trimethylsilyl)-2-dimethylamino-2-trimethylsiloxysilene (2) with a reversed Si=C bond polarity was formed through thermolysis of N,N-dimethyl(*tris*(trimethyl-silyl)silyl)methaneamide (1) in presence of alcohols. Surprisingly, no products resulting from reaction of the silene with the alcohol were observed, and this should represent the first example of a silene that is persistent to alcohols. The amide group of the silylamide is instead replaced by the alkoxy group. When thermolyses are performed in the presence of both an alcohol and a 1,3-diene, both the silylether and the [4+2] cycloadduct of the reaction between silene and diene are observed.

Indeed, the reaction of alcohols with N,N-dimethyl-(*tris*(trimethyl-silyl)silyl)methaneamide represent a new base-free pathway for protection of alcohols with the *tris*(trimethyl-silyl)silyl group, a group that has shown to be a fluoride resistant but photochemically removable protecting group of alcohols.³⁸ Two other silylamides were also tested in the reaction of base-free alcohol protection chemistry and found to give positive results. In conclusion, silylamides provide advantages compared to existing alcohol protecting reagents since they allow for base and catalyst free conditions, and their reactions give either solvent (DMF) or other easily removable and benign by-products. The conversions/yields are high to excellent, and the smallest silylamide (10) used shows high selectivity for primary alcohols.

Acknowledgements

We first acknowledge Dr. Patrick Steel for many stimulating discussions on the topics of silenes and alcohol protections. Financial support from the Swedish Research Council (Vetenskapsrådet) is gratefully appreciated.

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