Organosilane-Induced Synthesis and Functionalization of Sulfur-Containing Compounds

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Reactions of organothiosilanes with organic substrates generally lead to delivery of a sulfur moiety onto the target molecule, the precise outcome being related to the structure of the silyl sulfide used. Aromatic and aliphatic silyl sulfides react with carbonyl compounds under acidic or basic conditions to afford thioacetals and thioketals, but reactions with more activated compounds such as α,β-unsaturated acylsilanes give the Michael adducts, which represent versatile intermediates in organic synthesis. Silyl sulfides can also participate in substitution reactions of silyl enol ethers to afford vinyl sulfides. On the contrary, hexamethyldisilathiane reacts with various carbonyl compounds under the catalysis of $CoCl_2{\cdot}6H_2O$ or $CF_3SO_3SiMe_3$ with thionation of the carbonyl unit, thereby providing a general access to thioketones and thioaldehydes, which can be trapped in situ by dienes. The use of $CF_3SO_3SiMe_3$ in the reaction with cyclohexadiene gives rise to the interesting feature that stereopredetermined access to either the *endo* or the *exo* isomer can be obtained. Furthermore, when using aromatic or heteroaromatic *o*-azidoaldehydes, the reactivity of hexamethyldisilathiane may be finely tuned to drive the reaction towards the synthesis of *o*-azidothioaldehydes, fused isothiazole ring systems, or aromatic and heteroaromatic *o*-amino aldehydes and *o*-amino thioaldehydes. Lastly, by taking advantage of the high reactivity of the C–Si bond under fluoride ion catalysis, selective regiospecific thiophilic functionalizations of thioketones, dithioesters, trithiocarbonates, and their sulfines by various organosilanes such as allylsilanes, benzylsilane, and α-hetero-substituted silyl nucleophiles can be realized.

Introduction

Organic sulfur compounds play key roles in many chemical and biochemical processes. This fact has prompted widespread investigations over the years, as a result of which such compounds have emerged as extremely versatile intermediates in organic synthesis. On the contrary, organic derivatives of silicon do not occur in nature, but the enormous advances in their chemistry over the last decades has led to a much improved knowledge of their utility in synthetic organic chemistry.[1]

In this context, it is not surprising that the chemistry of molecules containing both elements has also attracted a great deal of attention.[2] Formally similar to thiols, silyl

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sulfides exhibit very special behaviour. The unique as well as complementary properties and reactivities of S and Si make silyl sulfides a still developing class of organometallic compounds, the chemistry of which has yet to be fully exploited.

The driving force behind the reactivity of organosilanes usually stems from the strength of the Si−O single bond (ca. 106 kcal/mol). In combination with the relative weakness (ca. 70 kcal/mol) and high polarizability of the Si−S bond, this provides the main rationale for the reactivity of thiosilanes towards nucleophilic species, and renders these reagents useful as synthetic tools for several interesting chemical transformations.[3] For instance, silyl sulfides readily react with oxygen nucleophiles, such as water or alcohols, undergo addition to polarized double bonds, and can react with reagents possessing a soft electrophilic centre.

Due to their peculiar reactivity, organosilicon derivatives of sulfur have recently emerged as useful synthetic intermediates and their applications in the search for alternative synthetic strategies and the development of novel molecular structures have been steadily growing. Aspects of this chemistry are reviewed herein

Organosilane-Based Transfer of Sulfur Functionalities

The combination of a strong oxygenophile and a strong nucleophile in the same molecule renders alkyl and aryl thiosilanes very good reagents for carbonyl functionalization. Thus, they react with activated carbonyl compounds through cleavage of the Si−S bond and addition to the C=O unit.

Ethylthiotrimethylsilane, for instance, reacts slowly with chloral to give a 1:1 insertion product,[4] while methylthiotrimethylsilane adds to hexafluoroacetone under similar conditions.[5] Phenylthiotrimethylsilane reacts analogously, but requires even longer reaction times.[6]

Evans[7] found that methylthiotrimethylsilane reacts with aldehydes and ketones in the presence of trace amounts of Lewis acids at 0 °C to give dimethyl thioketals, that aromatic derivatives, such as PhSTMS, react only sluggishly at elevated temperatures, and that ethylthiotrimethylsilane is quite unreactive towards the same compounds. These findings suggest that, even with highly reactive carbonyl substrates, uncatalyzed thiosilane carbonyl addition is not a facile process. Carbonyl addition reactions of phenylthio- and ethylthiotrimethylsilane to aldehydes can also be efficiently catalyzed[8] by TBACN, TBAF, and KCN/18-C-6. However, such anions prove ineffective in the case of ketones. In general, phenylthiosilanes are somewhat less reactive than alkylthio derivatives towards carbonyl addition. Both alkylthio- and arylthiosilanes show high selectivity in additions to aldehydes. Under these conditions, α,β-unsaturated aldehydes and ketones react exothermically.

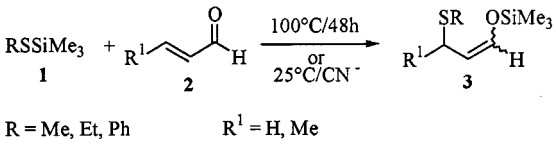
Acid catalysts such as zinc iodide, aluminium chloride, and anhydrous hydrogen chloride also promote carbonyl addition. In these cases, thiosilanes react rapidly with both aldehydes and ketones at room temperature to give *O*-trimethylsilyl hemithioacetals or ketals, respectively.[8] In the presence of a second equivalent of thiosilane, thioketals can efficiently be obtained. Alternatively, TfOTMS can be used at −78 °C to generate dithioacetals.[9]

Aldehydes can also be reacted with thiosilanes in the presence of 1-(trimethylsilyl)imidazole to give adducts,[10] in situ reduction of which with $LiAlH_4/AlCl_3$ affords the corresponding sulfides. Alternatively, such reactions can be performed in the presence of a catalytic amount of TMSCl/$InCl_3$ and Et_3SiH.[11]

Reactions of 2-phenylpropanal with phenylthiotrimethylsilane and [2,4,6-(trimethyl)phenylthio]trimethylsilane afford the corresponding dithioacetals. The diastereofacial selectivity of this α-chiral aldehyde in reactions with nucleophilic species has been evaluated.[12]

On the other hand, when aldehydes are treated with $PhSSiMe_3$ and a silyl ether in the presence of variable amounts of TfOTMS at dry ice temperature, *O*,*S*-acetals can be isolated.[13] Primary, secondary, tertiary, aromatic, as well as propargylic aldehydes can be efficiently reacted under these conditions.

Alkyl and aryl thiosilanes **1** are also known to react very slowly with α,β-unsaturated carbonyl compounds **2** at elevated temperatures. However, in the presence of cyanide, thiolate, or fluoride ions, the addition process occurs very efficiently[7] to regioselectively afford 1,4-adducts **3** as *E*/*Z* mixtures (Scheme 1). The same behaviour is observed in the presence of ZnI_2[7] or PPh_3.[14]



Scheme 1. Reactions of thiosilanes with α,β-unsaturated aldehydes

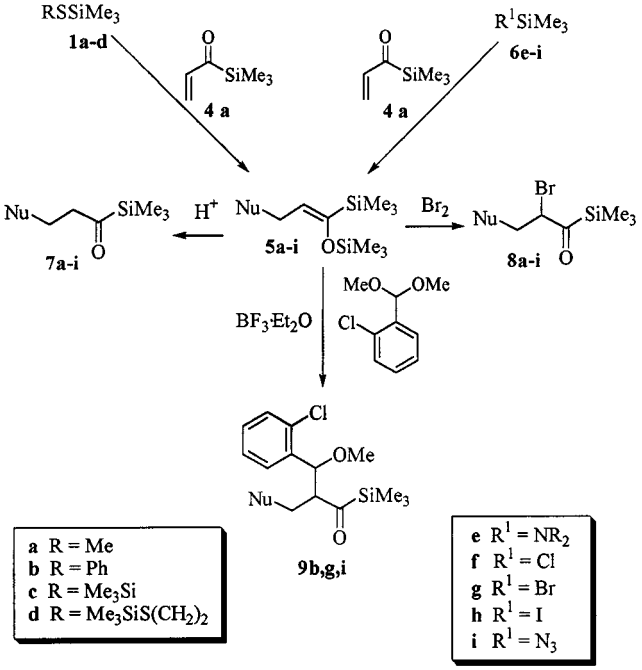
The function of the silicon moiety is most probably to drive the reaction in a regiospecific way, interaction of the silicon atom with the oxygen of the carbonyl unit leading to the development of a positive charge at the β-position.

In the presence of more activated carbonyl derivatives, such as α,β-unsaturated acylsilanes **4**,[15] a variety of silyl sulfides undergo uncatalyzed reactions to afford regiospecifically and stereoselectively ($E:Z > 95:5$) β-functionalized silyl enol ethers of acylsilanes **5a−d** in high yields (Scheme 2).[16]

This reactivity of α,β-unsaturated acylsilanes is not limited to silyl sulfides, but may be conveniently extended to various other silylated nucleophiles, such as amines **6e**, halosilanes **6f−h**, and trimethylsilyl azide **(6i)**, allowing access to a wide range of β-functionalized silyl enol ethers of acylsilanes **5e−i** (Scheme 2).

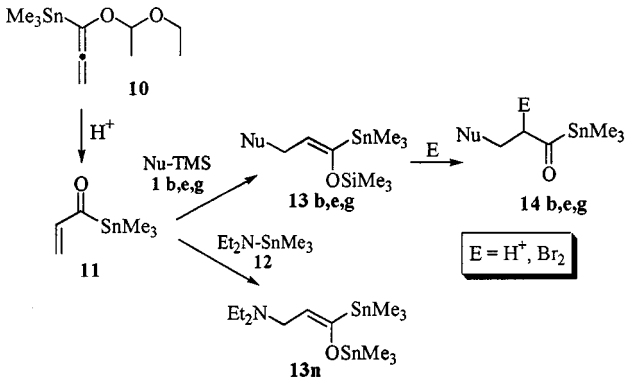
Acidic hydrolysis of compounds **5a−i** furnishes various β-functionalized acylsilanes **7** (Scheme 2), while with other electrophiles double in situ functionalization of the starting molecule can be achieved, leading to the polyfunctionalized acylsilanes **8** and **9** (Scheme 2).

Analogous reactivity can be observed with the parent tin derivative, propenoylstannane **11** (easily accessible through a modification of Reich's procedure,[17] by hydrolysis of the stannylated allenol **10**[18]). Propenoylstannane **11** reacts



Scheme 2. Organosilanes in the functionalization of propenoylsilane and reactivity of the obtained silyl enol ethers with electrophiles

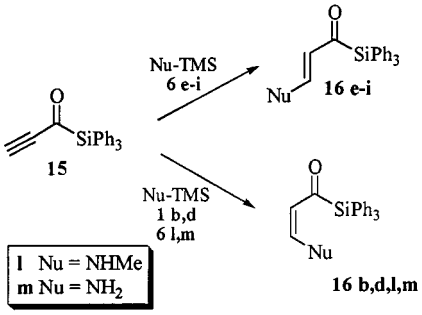
with silyl sulfide **1b**, other nucleophiles **1e**,**g**, and Et_2NSnMe_3 more rapidly than propenoylsilane, to afford silyl enol ethers **13b**,**e**,**g** and the stannyl enol ether **13n** of the acylstannane, respectively, again in a highly stereoselective fashion (Scheme 3). Further functionalization with electrophiles leads to propanoylstannanes **14b**,**e**,**g**.



Scheme 3. Synthesis and reactivity of propenoylstannane

The reactivities of propenoylsilane and -stannane complement each other well, allowing the introduction of either a tin or a silicon moiety at a selected position in a given target molecule.

Acetylenic silyl ketone **15** behaves similarly, reacting spontaneously with silyl sulfides **1b**,**d** (Scheme 4) and with other silylated nucleophiles **6e**−**m** (Scheme 4) to afford 1,4-addition products **16**.[19] Again, the additions proceed stereoselectively, but a notable change in this selectivity is seen, which appears to be strictly related to the nucleophile used. Thus, silylated secondary amines **6e**, halogens **6f**−**h**, and azide **6i** afford only the *trans* isomers **16e**−**i**, while silylated primary amines **6l**,**m** and silyl sulfides **1b**,**d** afford the *cis* isomers **16b**,**d**,**l**,**m**. In the case of primary and secondary amines, this behaviour can be rationalized in terms of initial formation of the *trans* isomer, followed by isomerization through a highly polar zwitterionic-type transition state.[20] The prevalence of *cis* orientation may be attributed to intramolecular hydrogen bonding, although a contribution from an N→Si interaction cannot be ruled out. Accordingly, the *cis* configuration found with silyl sulfides might be explained in terms of intramolecular stabilizing interactions, as observed previously for vinyl sulfides.[21]



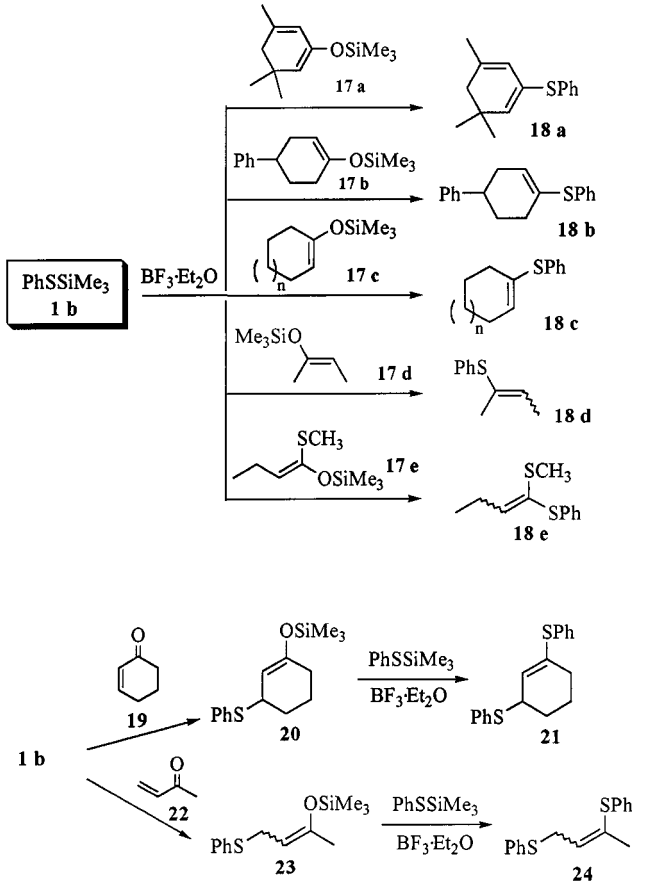
Scheme 4. Organosilanes in the regioselective functionalization of the acetylenic silyl ketone

Generally speaking, ethers can be cleaved by the action of a good oxygenophile and a strong nucleophile. Thus, the presence of both such functionalities in thiosilanes makes these compounds extremely useful reagents for this purpose. Under acid catalysis, selective cleavage of ether bonds can be achieved, allowing substitution of an alkyloxy group.[2] Both phenylthio- and methylthiotrimethylsilane have proved to be efficient agents for cleaving ether bonds, as has 1,2-ethanedithiobis(trimethylsilane).[22]

Silyl enol ethers can also undergo substitution through reaction with phenylthiotrimethylsilane in the presence of $BF_3{\cdot}Et_2O$, thereby providing a general access to substituted vinyl sulfides, which represent valuable synthetic intermediates as "masked carbonyl compounds" or as synthetic equivalents of enolonium ions, through a process involving nucleophilic substitution at a vinylic position (Scheme 5).[23]

The reaction is general and proceeds smoothly with various substrates ranging from linear to cyclic enol ethers, thus allowing access to a wide variety of enol thioethers.[24] It is also regiospecific, as illustrated by the synthesis of **18a**,**b**, but lacks stereoselectivity, compounds **18d**,**e** being obtained as a mixture of *E*/*Z* isomers (Scheme 5). Moreover, since silyl enol ethers are easily available from virtually all kinds of carbonyl compounds,[1] this procedure acquires a truly broad generality. For example, compound **18a** and the mixed vinyl thioketal **18e** are not easily accessible through established procedures.

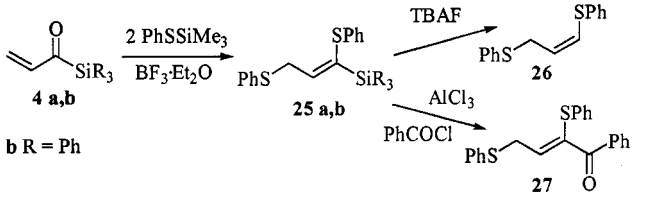
An even more valuable extension of this reactivity may be realized by reacting α-enones **19** and **22** with 2 equivalents of phenylthiotrimethylsilane (Scheme 5). An initial Michael-type addition of these compounds smoothly affords the functionalized silyl enol ethers **20** and **23**, which can subsequently be converted to the corresponding 1,3-



Scheme 5. Reactions of phenylthiosilane with silyl enol ethers: synthesis of vinyl sulfides

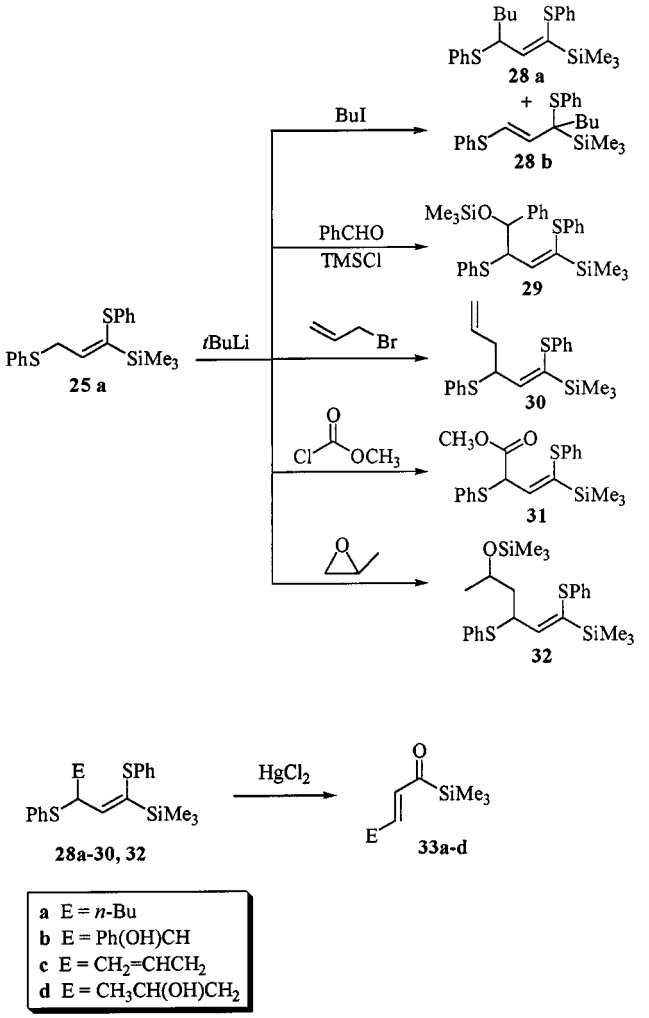
bis(phenylthio)propenes **21** and **24**, synthetic equivalents of β-acyl vinyl anions.[25]

Application of this methodology to α,β-unsaturated acylsilanes **4a**,**b** (Scheme 6) has allowed the development of a novel synthetic protocol.[26] Thus, treatment of compounds **4a**,**b** with two equivalents of $PhSSiMe_3$ affords, in the first step, β-functionalized silyl enol ethers, which can then be stereoselectively converted to the corresponding 1,3-bis(phenylthio)propenes **25a**,**b**. In this case, the silyl moiety not only serves to determine the stereoselectivity, but can also be easily removed with retention of configuration to give (*Z*)-1,3-bis(phenylthio)propene **26**. This represents an alternative and stereospecific synthesis of this valuable compound.



Scheme 6. Stereoselective synthesis of 1,3-bis(phenylthio)propenes

Alternatively, compounds **25a**,**b** may undergo $AlCl_3$-catalyzed reactions with acyl chlorides, thereby furnishing the functionalized bis(phenylthio)propene **27** with (*Z*) stereochemistry (Scheme 6).

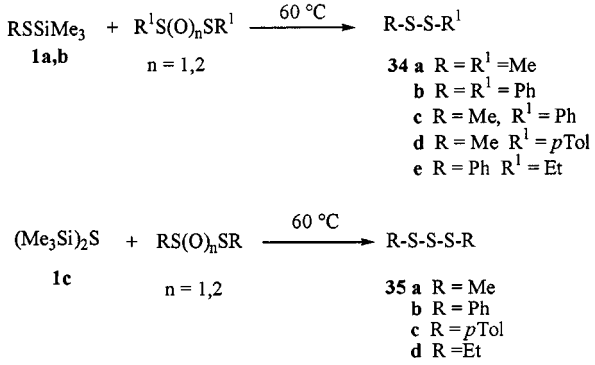


Scheme 7. Functionalization of 1,3-bis(phenylthio)-1-trimethylsilylpropenes with electrophiles and their behaviour as sila β-acyl vinyl anions

Treatment of compound **25a** with *t*BuLi and subsequent reactions of the resulting anion with electrophiles such as butyl iodide, aldehydes, methyl chloroformate, allyl bromide, and propene oxide illustrate its behaviour as a synthetic equivalent of a sila β-acyl vinyl anion; clean and regiospecific functionalization of the C-3 carbon can be achieved (Scheme 7).[26] The only exception to this behaviour is seen in the case of butyl iodide, where a 70:30 mixture of the two regioisomers **28a**,**b** is produced. Notably, not even generation of the allylpotassium derivative under superbasic conditions (*t*BuOK/BuLi), which have been reported to be conducive to the generation of chain-elongated primary compounds upon reaction with electrophiles,[27] offered any improvement of the regioisomeric ratio. All the obtained compounds were (*Z*) isomers, with the exception of **28b**.

Further reactions of sulfides **28a**−**30** and **32** with $HgCl_2$ afford the corresponding β-functionalized α,β-unsaturated acylsilanes **33a**−**d** under mild conditions (Scheme 7).[28] However, repeated attempts to react **31** with both $HgCl_2$ and copper(I) triflate did not lead to the desired β-methoxycarbonyl-functionalized acylsilane.

Thiosilanes also react with sulfoxides, which results in reduction to sulfides.[29] Unsymmetrical disulfides can be obtained through reactions of $MeSSiMe_3$ and $PhSSiMe_3$ with thiosulfinates and thiosulfonates (Scheme 8).[30]



Scheme 8. Thiosilane-based synthesis of disulfides and trisulfides

Reactions of arylthiosilanes with aryl thiosulfonates afford the expected unsymmetrical disulfides **34a−e**, together with variable amounts of the symmetrical disulfides.[31] Qualitative and quantitative analyses of such reaction mixtures by means of ^{13}C NMR spectroscopy[32] revealed that interchange reactions occur between the arylthiosilane and the disulfides, while, under the same conditions, the corresponding alkyl thiosilanes proved to be unreactive.

Reactions of aryl alkyl disulfides with arylthiosilanes exhibit a particular selectivity in that only exchange of arylthio moiety is observed. This has been demonstrated by reacting [D_5]phenylthiotrimethylsilane with phenyl methyl disulfide. Other *p*-substituted aromatic thiosilanes show the same selectivity upon reaction with aryl alkyl sulfides.

When hexamethyldisilathiane (HMDST) **1c** is reacted with thiosulfinates and thiosulfonates, the corresponding symmetrical trisulfides **35a−d** are obtained (Scheme 8).[33] The mild, neutral conditions prevent any decomposition of the obtained trisulfides to the corresponding disulfides or to higher polysulfides.

Synthesis of Thiocarbonyl Compounds using Hexamethyldisilathiane

Much of the interest in the synthesis and reactivity of thioketones stems from the fact that sulfur derivatives in general, and especially compounds containing a thiocarbonyl unit, have in recent years gained ever increasing importance in synthetic organic chemistry.[34a−34d] This was formerly due to their rich and interesting photochemical reactivity,[35] but more recently greater emphasis has been placed on the fact that such compounds have been identified as key intermediates in the synthesis of complex molecular systems exhibiting significant biological activity.[36] Not surprisingly, recent years have witnessed increasing development of novel synthetic procedures for their preparation and an extensive exploration of their synthetic potential.[2]

Several methods, ranging from pyrolysis to photochemical techniques, have been reported in the literature for the synthesis of thioketones, and their chemistry has been extensively studied.[37] However, direct conversion of carbonyl units into their corresponding thiocarbonyl analogues remains the most useful approach (H_2S/HCl or Lawesson's reagent).[37,38]

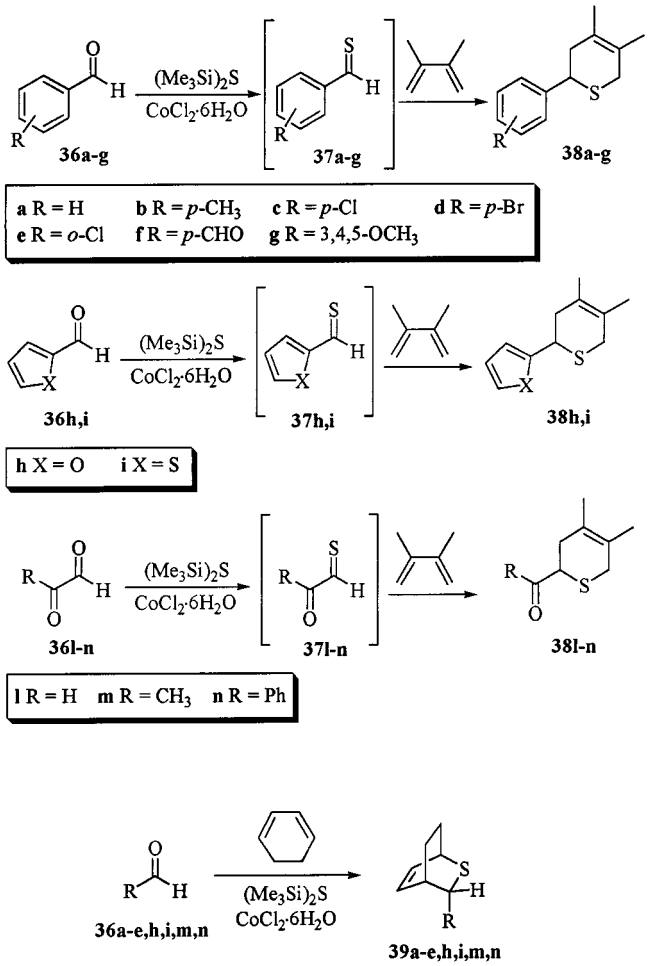
In contrast, simple thioaldehydes[34e,34f] had been considered as elusive compounds until Vedejs et al., through the photochemical cleavage of phenacyl sulfides,[39] and Krafft et al., through the fluoride ion induced elimination of α-silyl disulfides,[40] developed synthetically useful methods for their preparations and reported on their application in efficient and synthetically useful chemical reactions.

Several other groups have described Diels−Alder reactions of thioaldehydes generated thermally or by various elimination reactions.[41] Alternative methods for their preparation have also been reported, such as the butyllithium-catalysed conversion of aldehydes with hexamethyldisilathiane[42] or the fragmentation of dithiolane *S*-oxides.[43]

As observed for alkylthio- and arylthiosilanes, reaction of HMDST with carbonyl compounds is again a favourable process, the driving force still being the formation of the Si−O bond. Such reactions generally lead to thiocarbonyls under mild conditions. For example, HMDST reacts with aldehydes at 50−80 °C with formation of hexamethyldisiloxane (HMDSO) and the corresponding thioaldehydes as trimers.[44] Unlike linear derivatives, cyclic silathianes react with aldehydes only at higher temperatures (140−150 °C) and require ZnI_2 as a catalyst. This seems to be a generally applicable strategy, and the yields are considerably enhanced if the reaction is carried out in the presence of a Lewis acid. Steliou et al. found that a stoichiometric amount of boron trichloride is similarly able to efficiently promote this process.[45] The sulfuration of carbonyl compounds by this in situ formed boron trisulfide is considerably more rapid and is usually quantitative, even for substrates that are reported to be inert to thionation by preformed B_2S_3 or by Lawesson's reagent. This is believed to be a consequence of the particular structure of the boron trisulfide produced, the organometallic sulfide serving only to transport sulfur.

Hexamethyldisilathiane has also been used as a sulfur transfer agent in the presence of various acid catalysts, such as $CoCl_2{\cdot}6H_2O$ or $CF_3SO_3SiMe_3$. In this way, a wide variety of thioaldehydes have been generated under mild conditions, which could then be trapped in situ by suitable reagents. Under these conditions, the efficiency of the thionation as well as the stereochemistry of the reaction products are strongly affected by the nature of the catalyst employed.[46]

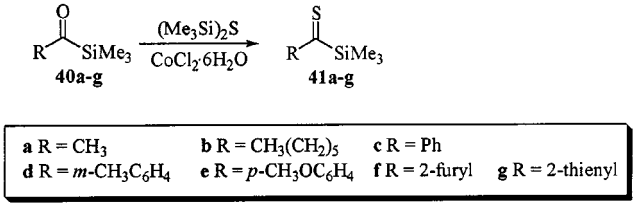
When aldehydes **36a−i** are treated with hexamethyldisilathiane in CH_3CN at room temperature in the presence of $CoCl_2{\cdot}6H_2O$, thioaldehydes **37a−i** are formed efficiently, as demonstrated by the high yields of the corresponding cycloadducts **38a−i** obtained by diene trapping (Scheme 9). Deleterious processes are minimized by the mild conditions of this protocol, under which the monomeric thioaldehydes, which are known to be rather prone to polymerization, have



Scheme 9. HMDST-based synthesis of thioaldehydes under $CoCl_2 \cdot 6H_2O$ catalysis

sufficient lifetimes to allow them to undergo further in situ reactions. Aromatic aldehydes and aldehydes bearing an electron-withdrawing substituent afford the corresponding adducts in excellent yields, making this method of thioaldehyde generation comparable to previously reported procedures. On the contrary, and not unexpectedly, most of the trapping reagents employed proved to be relatively unreactive with alkanethials, leading to low yields of adducts together with large amounts of oligomeric material.

Aldehydes are chemoselectively thionated in the presence of other carbonyl groups. Moreover, the reaction is equally efficient with compounds such as glyoxal **(36l)**, methylglyoxal **(36m)**, and phenylglyoxal **(36n)**, which were used as their hydrates or as commercial 40% aqueous solutions (Scheme 9).



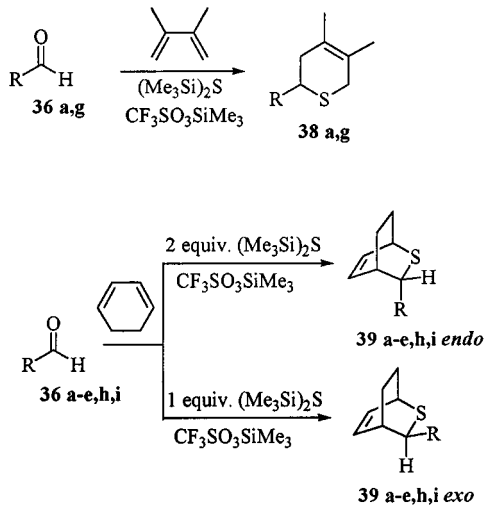
Scheme 10. Synthesis of thioacylsilanes

Reactions of thioaldehydes with cyclohexadiene proceed stereoselectively with formation of the *endo* adducts **39a−e,h,i,m,n**, with an *endo*/*exo* ratio usually greater than 95:5 (Scheme 9).[46,47]

The $CoCl_2 \cdot 6H_2O$-catalyzed thionation of carbonyl compounds even offers a convenient and simple approach[48] to a rather reactive class of thiocarbonyl compounds, namely the thioacylsilanes[49] **41a−g** (Scheme 10).

$CoCl_2 \cdot 6H_2O$ proved to be the most effective and mild catalyst, with $BF_3 \cdot Et_2O$ leading to more extensive oligomerization in the case of aromatic and aliphatic compounds, and to complete polymerization in the case of furoyl- and thienoyltrimethylsilane.

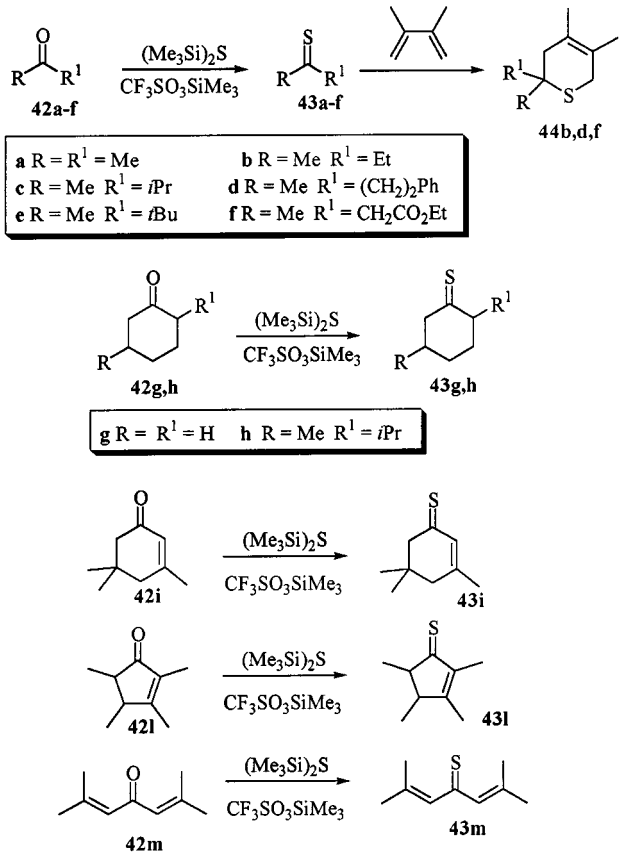
On the other hand, in the presence of the highly oxophilic agent $CF_3SO_3SiMe_3$, thionation proceeds well and thioaldehydes may be efficiently obtained (Scheme 11), although only under anhydrous conditions and in somewhat lower yields.[46]



Scheme 11. The use of silyl triflate in the HMDST-based thionation of aldehydes and its stereoselective implications

A unique feature of the use of TfOTMS as catalyst concerns the stereochemical outcome of the reactions with cyclohexadiene. The stereochemistry of the Diels−Alder adduct may be effectively selected so that the *endo* or the *exo* adduct can be obtained as the predominant diastereoisomer, simply by varying the molar ratio of the sulfurating agent. Thus, when a 2:1 ratio of $Me_3SiSSiMe_3$/aldehyde is used, the *endo* isomer is obtained selectively, while on using a 1:1 ratio the *exo* isomer is isolated as the predominant product (Scheme 11).

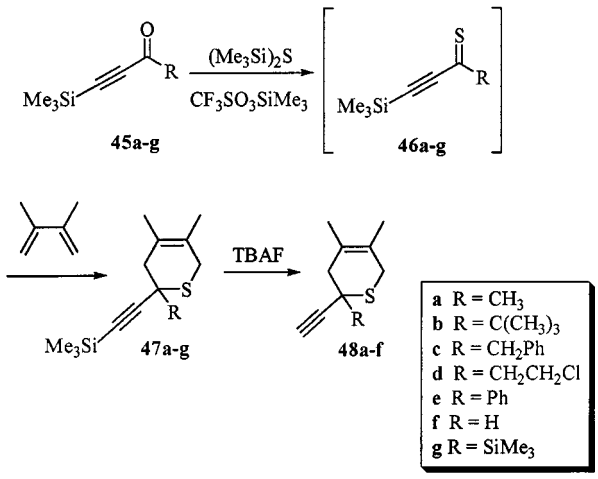
The greater efficiency of TfOTMS in promoting thionation processes as compared to $CoCl_2 \cdot 6H_2O$ is demonstrated by its ability to induce the thionation of less reactive derivatives such as ketones, furnishing the corresponding sulfur analogues **43a−h** (Scheme 12).[50] Although thioketones are, in fact, more stable than thioaldehydes, they still exhibit a great tendency to polymerize, unless sterically or electronically stabilized, highlighting the continued need to find milder conditions for their generation.



Scheme 12. HMDST-based thionation of ketones

As expected, the more reactive and less hindered ketones had to be trapped "in situ" as the corresponding cycloadducts **44** (Scheme 12), while more complex ones could be smoothly converted to the thio derivatives as monomers.

α,β-Unsaturated thioketones **43i−m** may also be obtained in this way, but in such cases, as already observed by Metzner and Vialle,[51] the β-position of the enone must be sterically hindered to avoid formation of the corresponding Michael adduct, which rules out any possibility of gaining access to unsubstituted thiocarbonyl compounds (Scheme 12).



Scheme 13. Synthesis of α,β-acetylenic thiocarbonyl compounds

Efforts to overcome these problems have focussed on the quest for suitable protecting groups. To this end, 3-trimethylsilyl acetylenic ketones **45a−e**, easily accessible from bis(trimethylsilyl)acetylene and the corresponding acyl chloride under Friedel−Crafts conditions,[52] have been considered. Thus, reactions of several 4-trimethylsilyl acetylenic ketones **45a−e** (Scheme 13) with HMDST in the presence of TfOTMS and dimethylbutadiene were found to afford the cycloadducts **47a−e** in generally good yields, proving the efficiency of the trimethylsilyl group in protecting the ynone moiety. This work represented the first general access to acetylenic thioketones.[53] $CoCl_2 \cdot 6H_2O$ proved inefficient in these reactions, leading only to complex product mixtures.

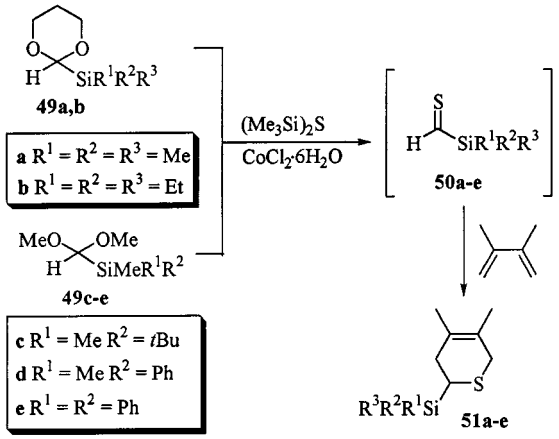
As an essential feature of an efficient protecting group, the trimethylsilyl moiety can easily be removed by simple treatment with aqueous TBAF, thus furnishing the unsubstituted acetylenic thioketones **48a−e** in practically quantitative yield (Scheme 13).

This reactivity can readily be extended to the synthesis of the first acetylenic thioaldehyde **46f**, as shown in Scheme 13.[54] Furthermore, with cyclohexadiene as the trapping agent, the reaction proceeds as well and, as observed previously, a selective access to either the *endo* or the *exo* isomer can be obtained.[53]

The conditions of this general protocol for the synthesis of acetylenic thioketones have also led to a simple access to the first acetylenic thioacylsilane (Scheme 13), which has been isolated as the cycloadduct **47g**.[55]

The versatility of the HMDST-based thionation of carbonyl compounds is further demonstrated by its application to the synthesis of another class of thiocarbonyl compounds, the thioformylsilanes. Despite the considerable synthetic potential of these compounds, they remain largely unexplored. Indeed, as far as we are aware, only one example has appeared in the literature. Thus, Vedejs et al.[56] generated such compounds by the photolytic fragmentation of phenacyl sulfides. Most probably, the difficulties in handling the formyl silanes owing to their very high sensitivity to molecular oxygen (iPr$_3$SiCHO ignites spontaneously in air)[57] has hitherto hampered a thorough study of their chemistry. This instability clearly prohibits their generation by direct thionation of formylsilanes, hence a different approach had to be used in this case. It has been found that silyl acetals, the precursors of the formylsilanes, can also function as good precursors of the desired thioformylsilanes. Thus, by treating these with HMDST in the presence of various silylated acetals **49a−e**, easily accessible by means of transacetalization reactions from the appropriate silyl dithianes, the corresponding thioformylsilanes **50a−e** could be obtained in good yields (Scheme 14).[58]

Both the 1,3-dioxanes **49a**,**b** and the dimethoxy derivatives **49c−e** constitute suitable starting materials, the choice simply depending on the volatility of the obtained acetals. Trapping with 2,3-dimethylbutadiene affords the cycloadducts **51** in good yields, showing that these silyl thioaldehydes are quite reactive as compared to their aliphatic counterparts, which are known to be rather inert towards

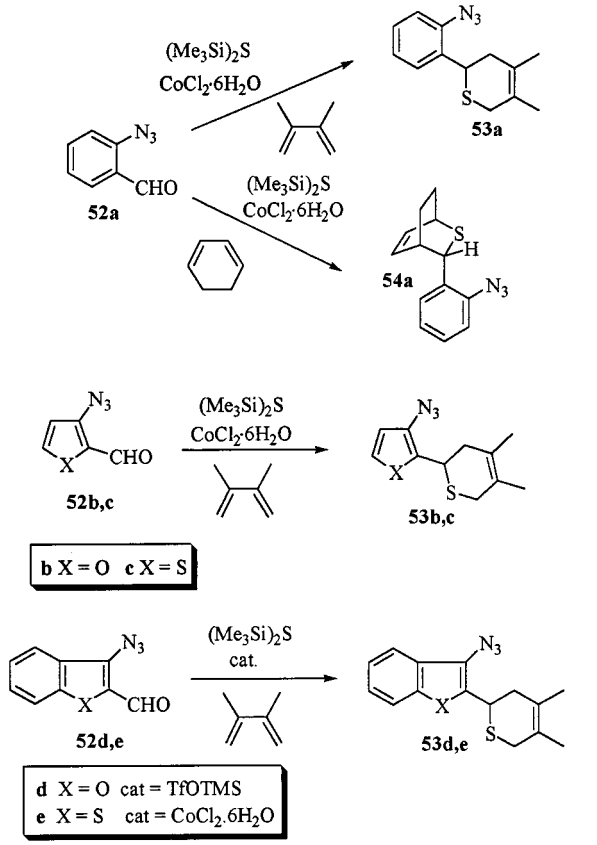


Scheme 14. HMDST in the generation of thioformylsilanes

Diels–Alder cycloadditions. In reactions with cyclohexadiene as the trapping agent, no traces of the *exo* isomer were detected in the crude reaction mixtures, except in the case of the trimethylsilyl derivative **50a**, where a 95:5 *endo*/*exo* mixture was obtained. On the other hand, using $CF_3SO_3SiMe_3$, a stereodefined entry to both the *endo* and *exo* isomers could be developed. Thus, by employing two equivalents of HMDST, a 95:5 ratio of *endo*:*exo* isomers was obtained, while with just one equivalent the selectivity was shifted in favour of the *exo* isomer, although in the latter case, in contrast to previous observations, only a slight prevalence of the *exo* compound was detected.

Reactions of α-Azido Aldehydes with Hexamethyldisilathiane

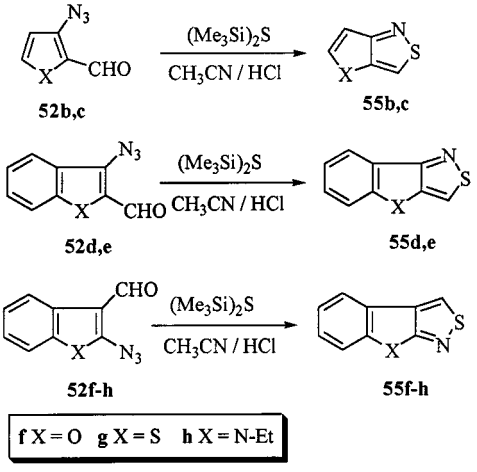
HMDST thionation appears to be highly chemoselective, thus making this protocol compatible with various functionalities that one might want to incorporate in the target molecule. This is of interest with regard to the reactions of functionalized aldehydes, such as aromatic and heteroaromatic α-azido derivatives. The presence of an azido function provides an attractive additional site for further functionalization, thus expanding the synthetic potential of such compounds. Moreover, due to its intrinsic structure, the azido group seemingly represents a good trapping agent for the transient thioaldehydes. Indeed, the thermolysis of aryl and heteroaryl azides bearing α,β-unsaturated *ortho*-substituents represents a known convenient route for the synthesis of various fused azoles,[59] although only one report has appeared in the literature concerning intramolecular cyclizations involving azides and adjacent thiocarbonyl substituents.[60] Thus, reactions of *o*-azidobenzaldehyde **(52a)** with HMDST in the presence of dimethylbutadiene or cyclohexadiene gave the corresponding thioaldehyde adducts **53a** and **54a** in fairly high yields (Scheme 15).[61] Under similar conditions, the heteroaromatic azido aldehydes **52b–e** also reacted in the presence of the trapping agent to afford functionalized dihydrothiopyrans **53b–e** (Scheme 15). However, the mild catalyst $CoCl_2·6H_2O$ was found to be rather ineffective in promoting the thionation of 3-azido-2-formylbenzofuran **(52d)**. In this case, a satisfactory yield of the corresponding thiopyran could be obtained by using a stronger Lewis acid such as $CF_3SO_3SiMe_3$, or by performing the reaction in neat diene.



Scheme 15. Selective generation and trapping of *o*-azido thioaldehydes

Attempts to carry out this reaction with the 2-azido-3-formyl derivatives **52f–h** proved unsuccessful, leading only to unidentified products. These probably resulted from ring-cleavage fragmentation of the initially formed azido adducts.

On changing the catalyst to the stronger HCl, the azido group itself can act as an efficient thioaldehyde trapping agent, thus offering a novel practicable route to fused isothiazole ring systems **52f–h** (Scheme 16).[62]



Scheme 16. Intramolecular trapping of *o*-azido thioaldehydes: direct access to fused isothiazoles

Under these conditions, 3-azido-2-formylthiophene **(52c)**, 3-azido-2-formylbenzo[*b*]thiophene **(52e)**, and 2-azido-3-formylbenzo[*b*]thiophene **(52g)** may be efficiently reacted (Scheme 16), allowing selective access to the hitherto unknown isomeric thieno- and benzothienoisothiazoles **55c**,**e**,**g**.[63] The synthesis of these compounds can conceivably be attributed to decomposition of the intermediate *o*-azidothioaldehyde, resulting in the preferred formation of cyclized isothiazoles. This would appear to hold true even in the case of the α-heteroaryl azides, which are known to decompose through smooth ring-opening.

Under similar conditions, reactions of 3-azido-2-formylfuran **(52b)** and -benzo[*b*]furan **(52d)** afforded the fused isothiazoles **55b**,**d**, albeit in lower yields (Scheme 16). On the other hand, 2-azido-3-formylbenzo[*b*]furan **(52f)** did not give any isolable isothiazole. This contrasting behaviour can be attributed to greater instability of the resulting furoisothiazoles compared to thienoisothiazoles under the acidic conditions used.

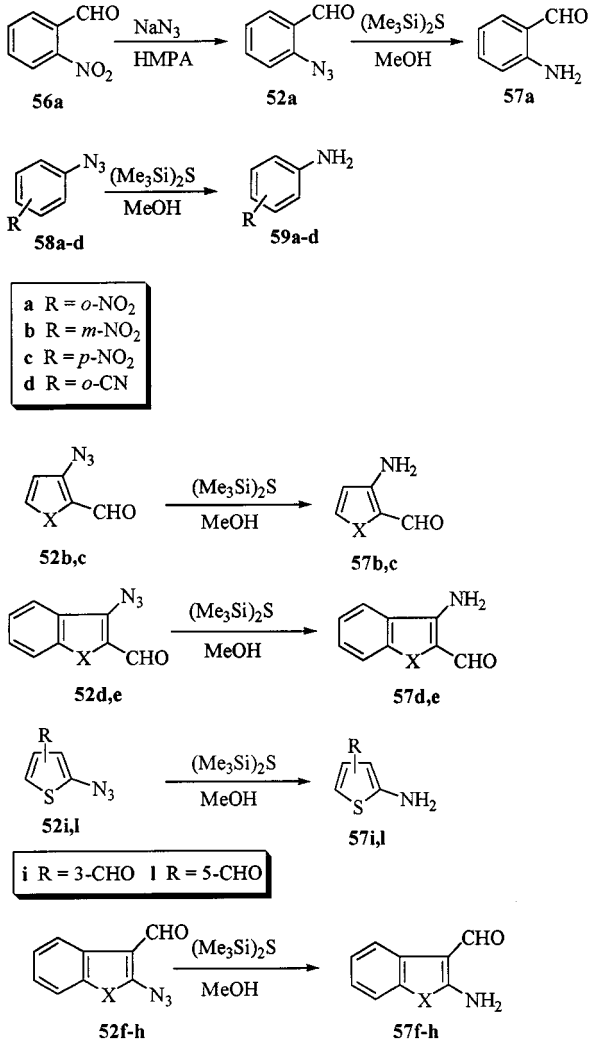
A peculiar behaviour was found with the azido indole **52h**, which afforded a 60:40 mixture of the 2-amino-3-thioformyl derivative and isothiazole **55h** in good overall yield (Scheme 16). This result suggests that in this case reduction of the azido group competes with thionation of the formyl moiety.

In contrast to the heteroaromatic azides, *o*-azidobenzaldehyde **(52a)** led exclusively to the *o*-azidothiobenzaldehyde trimer, indicating that in this case the intermediate azidothiobenzaldehyde undergoes preferential trimerization rather than intramolecular cyclization to isothiazole. The greater aromatic character of the benzene ring as compared to the heteroaromatic rings outweighs all other factors, ruling out the azide cyclization process and allowing only the oligomerization reaction.

Furthermore, by changing the reaction conditions, e.g. by treating *o*-azidobenzaldehyde **(52a)** with HMDST in methanol in the absence of any added catalyst, a fine tuning of the reactivity of HMDST may be achieved, leading to selective reduction of the azido function (Scheme 17).[64]

Moreover, since *o*-azidobenzaldehyde **(52a)** is quantitatively available by direct reaction of *o*-nitrobenzaldehyde **(56a)** with sodium azide in HMPA (Scheme 17), this easy two-step procedure represents a convenient methodology for the formation of *o*-aminobenzaldehyde **(57a)** from the corresponding nitro derivative. It is known that reductions of *o*-nitrobenzaldehydes to amino aldehydes are complicated by competing inter- and intramolecular condensation reactions of the intermediate hydroxylamines, which often renders the choice of reducing agent critical.

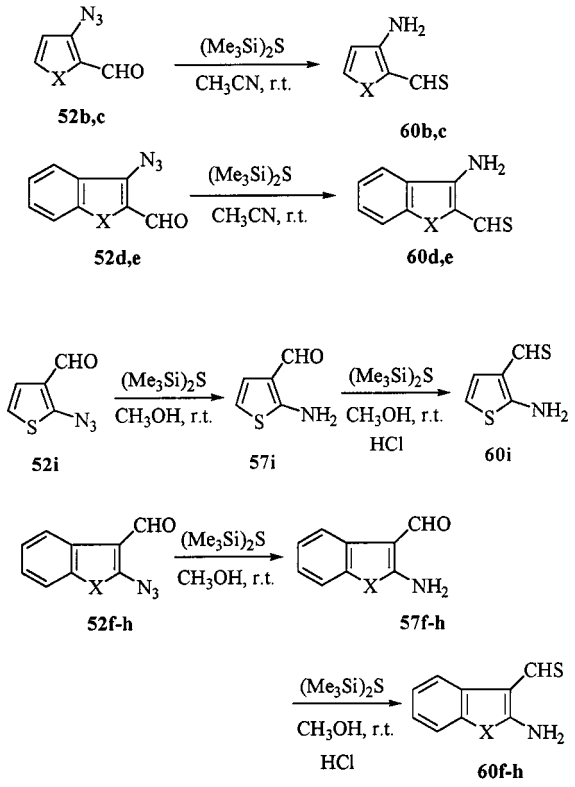
A similar procedure can be efficiently applied to several aromatic azides bearing electron-withdrawing substituents, **58a−d** (Scheme 17), thus providing a simple and high-yielding methodology for the formation of amines. This method is especially useful for the selective reduction of *o*-azido- to *o*-amino aldehydes, which are important starting materials for the construction of annulated heterocyclic systems.



Scheme 17. HMDST-selective reduction of the azido moiety: a facile access to *o*-amino aldehydes

Interestingly, this reactivity can be efficiently extended to the heteroaromatic derivatives **52b−l**, leading in all cases to a smooth reduction of the azido function (Scheme 17).

A further point of interest concerning the reaction of HMDST stems from a combination of the already observed characteristics, in that it can bring about the direct conversion of *o*-azidoaldehydes to chemically stable *o*-amino thioaldehydes. In fact, since the first preparation of a stable monomeric pyrrolecarbothioaldehyde, reported by Woodward et al. in 1960,[65] it has become apparent that the highly reactive thioformyl moiety can be effectively stabilized by the mesomeric effect of an electron-rich heterocyclic ring or a carbon−carbon double bond. Indeed, other stable carbothioaldehydes, often derived from the pyrrole ring[66] or enamino systems,[67] have since been reported, although they have been relatively few in number. More recently, Becher and co-workers[68] reported several *o*-aminocarbothioaldehydes belonging to the pyrazole and indole series, which represent additional examples of chemically stable heteroaromatic thioaldehydes that owe their stability to delocalization of the amino nitrogen lone pair.



Scheme 18. Synthesis of heterocyclic *o*-amino thioaldehydes

Thus, in the presence of a threefold excess of HMDST in CH_3CN, 3-azido-2-formylfuran **(52b)** (Scheme 18) undergoes a smooth reaction at room temperature to give the corresponding amino thioaldehyde **60b** via the intermediate amino aldehyde **57b**.[69] Following the same protocol, 3-azido-2-formylbenzo[*b*]furan **(52d)**, 3-azido-2-formylthiophene **(52c)**, and 3-azido-2-formylbenzo[*b*]thiophene **(52e)** could be similarly transformed into the respective amino thioaldehydes **60c−e** (Scheme 18) in 40−57% isolated yields. These findings show that, in contrast to earlier observations concerning experiments conducted in neat CH_3OH, in neat CH_3CN HMDST is effective in thionating the initially formed amino aldehydes. This clearly suggests that HMDST behaves as a more powerful thionating agent in the latter solvent than in the former.

In contrast to the reactions with the isomeric azidoaldehydes, HMDST in neat CH_3CN only converts 2-azido-3-formylthiophene **(52i)**, 2-azido-3-formylbenzo[*b*]furan **(52f)**, and 2-azido-3-formylbenzo[*b*]thiophene **(52g)** to the corresponding amino derivatives **57i** and **57f,g**, presumably as a consequence of the reduced reactivity of the formyl moiety in these compounds. Following the addition of HCl, the amino aldehydes thus obtained can undergo further reaction with HMDST to give rather complex mixtures containing only minor amounts of the desired amino thioaldehydes. Instead, satisfactory yields of these thioaldehydes were successfully isolated by means of an analogous procedure performed in CH_3OH rather than CH_3CN (Scheme 18).

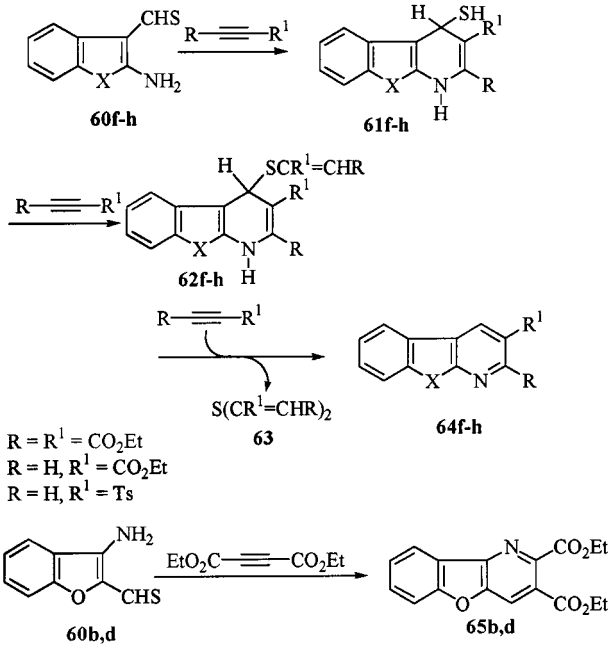
In the case of compound **60b**, restricted rotation of the thioformyl group was clearly evident from the ^1H NMR spectrum recorded in DMSO, which showed the presence of two thioformyl protons in ca. 1:1 ratio at δ = 10.38 and 10.29.

Furthermore, HMDST was found to be capable of converting 2-azido-1-ethyl-3-formylindole **(52h)** to the isolable amino thioaldehyde **60h** in good yield (Scheme 18).

In the same way as its heterocyclic analogues, *o*-azidobenzaldehyde **(52a)** was readily transformed by HMDST into *o*-aminothiobenzaldehyde, but this proved to be non-isolable owing to rapid trimerization (and polymerization) reactions of its thioformyl moiety. Predictably, in such cases the aromatic character of the benzene ring prevents adequate stabilization of the thioformyl function.

Heteroaromatic amino thioaldehydes **60b−d,f** have also been subjected to NMR conformational investigations[70] and the barriers to rotation about the Ar−CHS carbon−carbon bond and the adjacent Ar−NH_2 carbon−nitrogen bond have been determined.

Interestingly, the *o*-amino thioaldehydes obtained in this way are amenable to further reactions with activated acetylenic derivatives, which allows a novel access to *b*-fused pyridine ring systems. Thus, for example, on reacting 2-amino-3-thioformylbenzofuran, indole and thiophene **57f−h** with diethyl acetylenedicarboxylate, a smooth entry to the diethyl carboxylate derivatives of the parent pyridine fused systems **64f−h** may be achieved (Scheme 19).[71]



Scheme 19. Reactivity of heterocyclic *o*-amino thioaldehydes with activated acetylenic derivatives: simple access to fused pyridine ring systems

Treatment of 2-amino-3-thioformylbenzo[*b*]furan **(57f)** with three equivalents of diethyl acetylenedicarboxylate in benzene at room temperature and subsequent heating to 110 °C in vacuo furnished the pyridine **64f**. Its generation can be rationalized in terms of initial formation of the thiol intermediate **61f**, reaction of this with the alkyne to give the vinyl sulfide **62f**, and subsequent aromatization to the *b*-fused pyridine **64f** with formal elimination of an

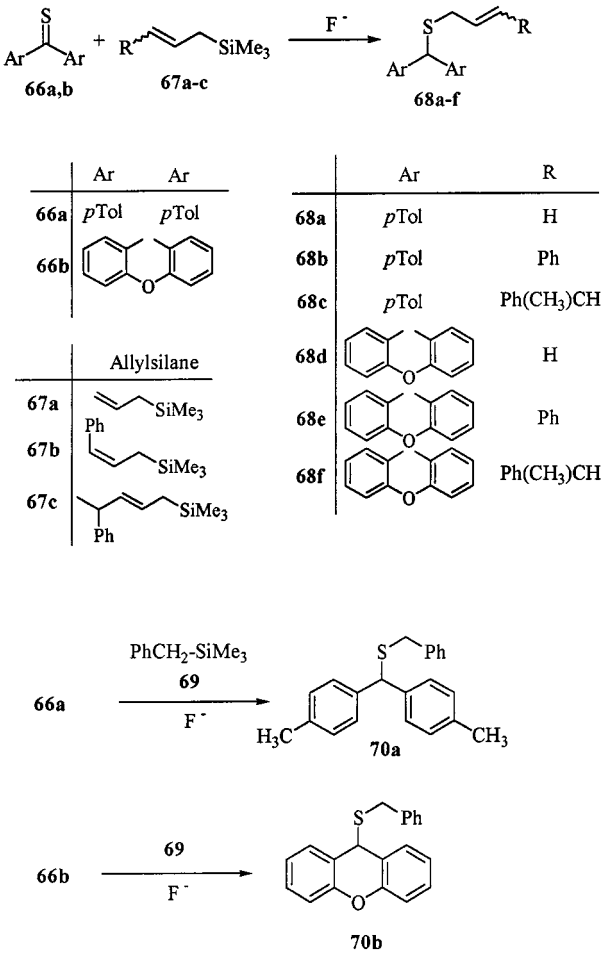
$HSC(CO_2Et)=CHCO_2Et$ unit. The latter was trapped by the alkyne to give the sulfide **63**, which could be isolated.

In similar one-pot procedures, 2-amino-1-thioformylbenzo[*b*]thiophene **(57g)** and 2-amino-1-ethyl-3-thioformylindole **(57h)** also reacted with diethyl acetylenedicarboxylate to give the corresponding disubstituted pyridines **64g**,**h** in moderate yields (Scheme 19). As with the amino aldehydes **57f−h**, treatment of 3-amino-2-thioformylbenzo[*b*]furan **(60b)** and 3-amino-2-thioformylfuran **(60d)** with diethyl acetylenedicarboxylate furnished the isomeric fused pyridines **65b**,**d** in useful yields (Scheme 19).

Additionally, with methyl propiolate and *p*-toluenesulfonylacetylene, the thioaldehydes **57f−h** could be similarly converted to the 3-functionalized benzofuro[2,3:*b*]pyridines and indole[2,3:*b*]pyridines in comparable yields, although longer reaction times were generally required (Scheme 19).

In these last cases, only the 3-substituted isomers were obtained, showing this to be a regiospecific route to functionalized pyridine ring systems.

On the other hand, the amino thioaldehyde **60f** was found to be unreactive towards poorly electrophilic alkynes (trimethylsilylacetylene and hex-1-yne) and electron-deficient alkenes (dimethyl fumarate and maleate), even in refluxing benzene.



Scheme 20. Regioselective thiophilic functionalization of thioketones with silyl nucleophiles

Regioselective Functionalization of Thiocarbonyl Compounds using Organosilanes

The use of silicon to enhance nucleophilicity and its hard character combine to render trimethylsilyl nucleophiles extremely useful reagents in organic synthesis, as a consequence of which organosilanes have received a great deal of attention during the last decades. However, relatively few examples of their reactivity towards sulfur-containing molecules have been reported.

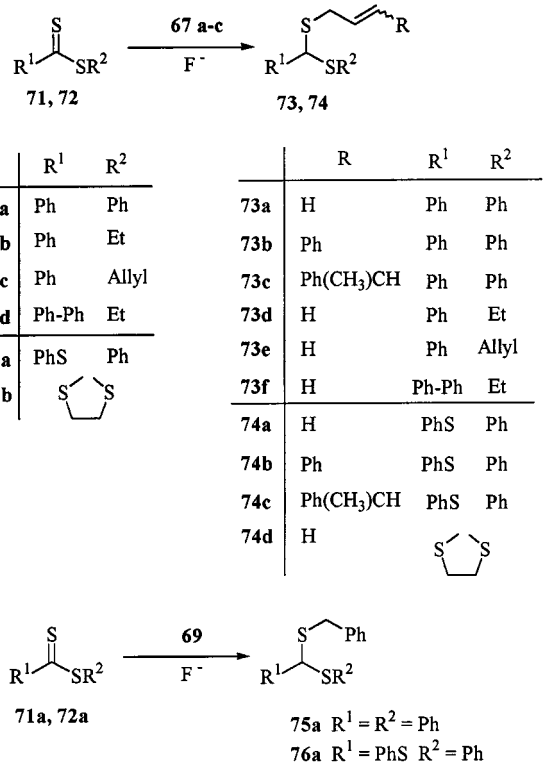
Reactions of thiocarbonyl compounds with organolithium, -sodium, and -magnesium derivatives are reported to lead mainly to thiophilic addition, in agreement with predictions of reversed polarity of the thiocarbonyl group as compared to the carbonyl function.[72] However, various other reactions such as carbophilic addition, reduction, double addition, and formation of ene sulfides proceed concurrently, thus greatly reducing the efficiencies of such reactions. On the contrary, additions of allylic Grignard reagents afford products derived from a direct carbophilic attack and a subsequent allylic shift.[73] The formation of *C*-allylated products without inversion of the allylic chain, as is observed in some cases,[74] has been rationalized in terms of an initial thiophilic addition followed by a [2,3]-sigmatropic rearrangement.

On the contrary, in the presence of fluoride ions, allylsilanes react smoothly with thiocarbonyl compounds to afford allyl sulfides, thus following a clean thiophilic pathway (Scheme 20).[75] This regiochemical outcome is opposite to that which has invariably been reported with other types of allylic organometallic reagents.[73c]

This reactivity appears to be related to the structure of the thiocarbonyl compound. Thus, while di-*p*-tolyl thioketone **(66a)** and thioxanthone **(66b)** afford good yields of allyl sulfides **68a−f**, thiocamphor proves to be rather unreactive owing to the well-known reluctance of this particular thioketone to react in its thiocarbonyl form as opposed to its enethiol form.

The structure of the allylsilane also plays a crucial role. For example, with γ-substituted allylsilanes **67b**,**c**, a retardation of the reaction rate is noticed and no allyl shift has ever been observed. Nevertheless, the only by-products were ketones arising from decomposition of the starting thiones, which were observed in cases where extended reaction times were required.

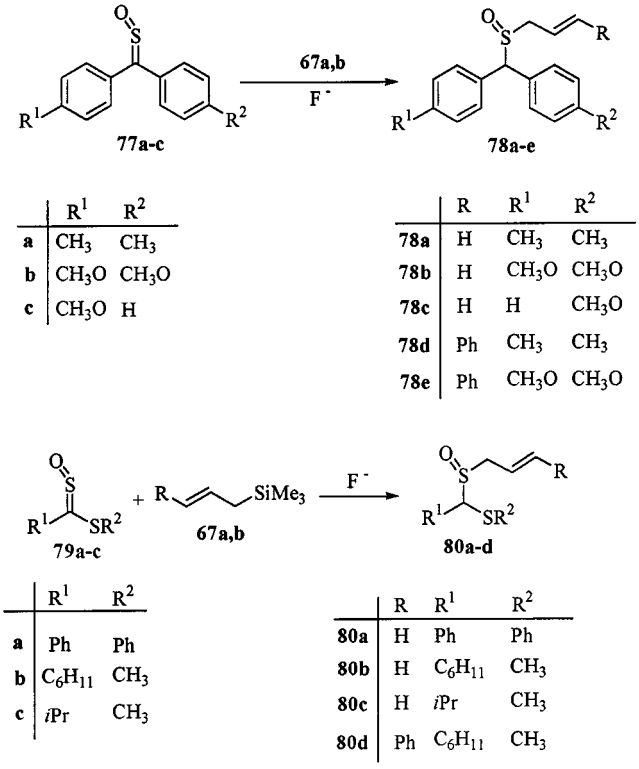
Tetrabutylammonium fluoride (TBAF) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) can be employed as fluoride ion sources. Both compounds have proved to be efficient in promoting the above reaction, although somewhat higher yields may be achieved using TBAF. On the other hand, the possibility of performing the reactions at much lower temperatures (−78 °C) with TASF becomes advantageous when dealing with rather sensitive substrates.[76]



	R^1	R^2
71a	Ph	Ph
71b	Ph	Et
71c	Ph	Allyl
71d	Ph-Ph	Et
72a	PhS	Ph
72b	S S	

	R	R^1	R^2
73a	H	Ph	Ph
73b	Ph	Ph	Ph
73c	$Ph(CH_3)CH$	Ph	Ph
73d	H	Ph	Et
73e	H	Ph	Allyl
73f	H	Ph-Ph	Et
74a	H	PhS	Ph
74b	Ph	PhS	Ph
74c	$Ph(CH_3)CH$	PhS	Ph
74d	H	S S	

Scheme 21. Reactions of organosilanes with dithioesters and trithiocarbonates



	R^1	R^2
a	CH_3	CH_3
b	CH_3O	CH_3O
c	CH_3O	H

	R	R^1	R^2
78a	H	CH_3	CH_3
78b	H	CH_3O	CH_3O
78c	H	H	CH_3O
78d	Ph	CH_3	CH_3
78e	Ph	CH_3O	CH_3O

	R^1	R^2
a	Ph	Ph
b	C_6H_{11}	CH_3
c	*i*Pr	CH_3

	R	R^1	R^2
80a	H	Ph	Ph
80b	H	C_6H_{11}	CH_3
80c	H	*i*Pr	CH_3
80d	Ph	C_6H_{11}	CH_3

Scheme 22. Synthesis of allyl sulfoxides through reaction of allylsilane with sulfines

The aforementioned inversion of regiochemistry with respect to the metal derivatives[72a] can also be observed with other silyl nucleophiles such as benzylsilane **69**, which reacts similarly to afford the corresponding benzyl sulfides **70a**,**b** in good yields (Scheme 20).[75]

The reaction can also be performed with other thiocarbonyl-containing compounds such as dithioesters **71a−d** and linear or cyclic trithiocarbonates **72a** or **72b** (Scheme 21).[77] As well as confirming the already observed inversion of the regiochemistry, these results show that a completely different pathway to that observed with allylic Grignard reagents is followed,[73] leading to the allylic bis(sulfides) **73a−f** and tris(sulfides) **74a−d** (Scheme 21). Substitutions of the R′S- moiety in dithioesters have never been observed.

Benzylsilane **69** behaves similarly, leading to the generation of benzyl bis(sulfides) **75a** and tris(sulfides) **76a** (Scheme 21).[77] This is in marked contrast to the reactions of dithioesters and trithiocarbonates with the corresponding organometallic reagents, which afford only the products of direct carbophilic attack.[72a,73b]

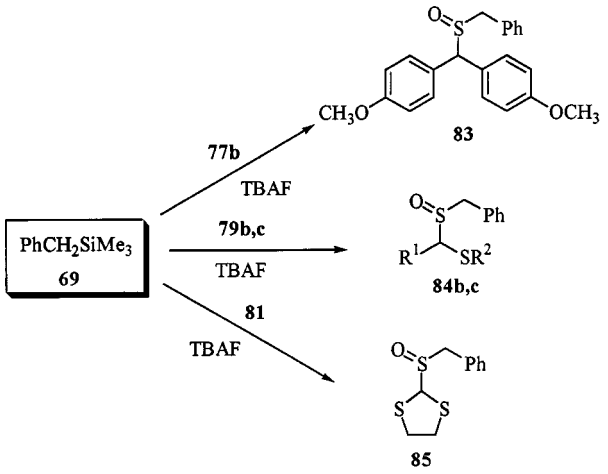
This methodology can also be applied to the structurally related *S*-oxides of thiocarbonyl compounds, namely sulfines, the chemical behaviour of which towards nucleophiles has been extensively studied by the groups of Zwanenburg[78a,78b] and Metzner.[78c] In the reactions of these heterocumulenic compounds with nucleophiles, the thiophilic *versus* carbophilic course of the reaction has been found to be dependent on the nature of the nucleophilic agent (lithium, sodium, or Grignard reagents) and on the substituents attached to the sulfine carbon atom.[79] Thiophilic attack is more frequently observed,[80] but some cases of carbophilic substitution on the sulfinyl carbon have been reported.[79,80a,80b] Thus, even though thiophilic addition with silyl nucleophiles may be predicted from consideration of the electron-poor character of the sulfur centre relative to carbon, the experimentally observed behaviour of known nucleophiles does not yet allow a correlation of S *versus* C addition in terms of the hard or soft nature of the reagent.

The reaction of diaryl sulfines **77a−c** with allylsilanes in the presence of anhydrous TBAF affords the corresponding allyl sulfoxides **78a−e** in good yields (Scheme 22),[81] showing again that thiophilic addition is preferred.

The reaction can also be conveniently extended to other types of sulfines, such as those of dithioesters **79a−c**[81] and trithiocarbonate **81** (Scheme 22),[82] which are converted to allyl sulfoxides **80a−d** and **82**, respectively. The products obtained from dithioesters are dithioacetal monoxides, which represent useful intermediates in that they are synthetic equivalents of acyl carbanions.[82]

It is interesting to note that aliphatic sulfines of enethiolizable dithioesters **79b**,**c**, which can easily be prepared under strictly controlled conditions,[83] also react under the aforementioned conditions.[81]

Sulfines also react with benzylsilane under the same conditions, allowing a smooth regiospecific transformation to



Scheme 23. Synthesis of benzyl sulfoxides

the corresponding benzyl sulfoxides **83**, **84b**,**c**, and **85** (Scheme 23).[82,83]

With the aim of introducing further reactive sites in the obtained molecules, this silicon-mediated functionalization has been extended to structurally more complex silyl derivatives such as α-hetero-substituted silyl nucleophiles.

The reaction of aromatic thioketone **66a** with (phenylthiomethyl)trimethylsilane **(86)** in the presence of anhydrous TBAF affords the corresponding dithioacetal **87**, thereby generating a polyfunctionalized molecule through a regiospecific thiophilic addition (Scheme 24).[84] Similarly, the aromatic sulfine **77b** affords the dithioacetal monoxide **90** (Scheme 24).

The reaction can also be performed with dithioesters **71b**,**c**, leading to the tris(sulfides) **88b**,**c**, and with the corresponding sulfines **79a**,**b** to give **91a**,**b**. In the latter case, it offers a regiospecific access to compounds **91a**,**b**, in which the position of the sulfoxide moiety can be predetermined (Scheme 24).

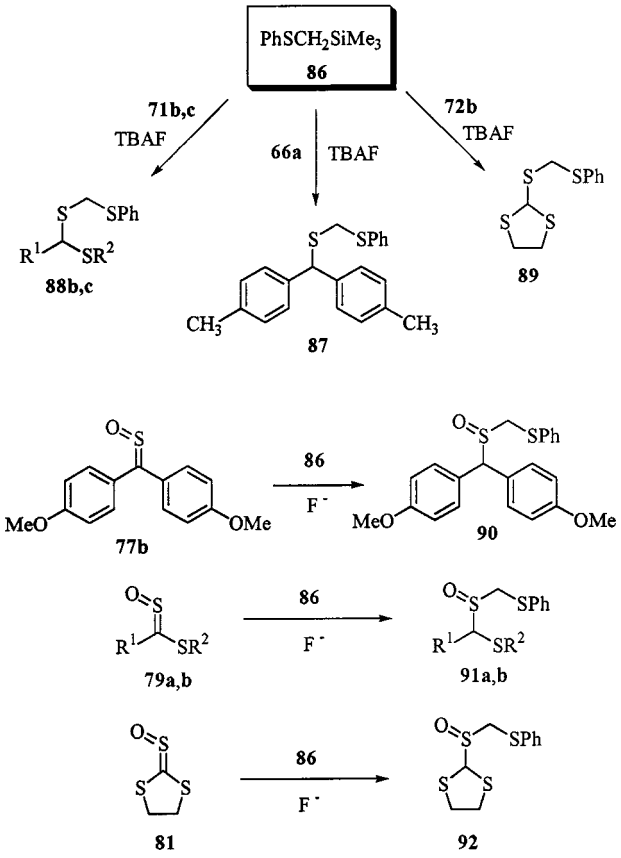
Trithiocarbonate **72b** and its sulfine **81** react similarly to afford the corresponding tetrasulfide **89** and the sulfoxide **92**, respectively (Scheme 24).[84]

The seleno derivative (phenylselenomethyl)trimethylsilane **(93)** also reacts, resulting in mixed selenothioacetals of thioketones **94**, of dithioesters **95**, and of trithiocarbonate **96** (Scheme 25), as well as of their corresponding sulfines.[84]

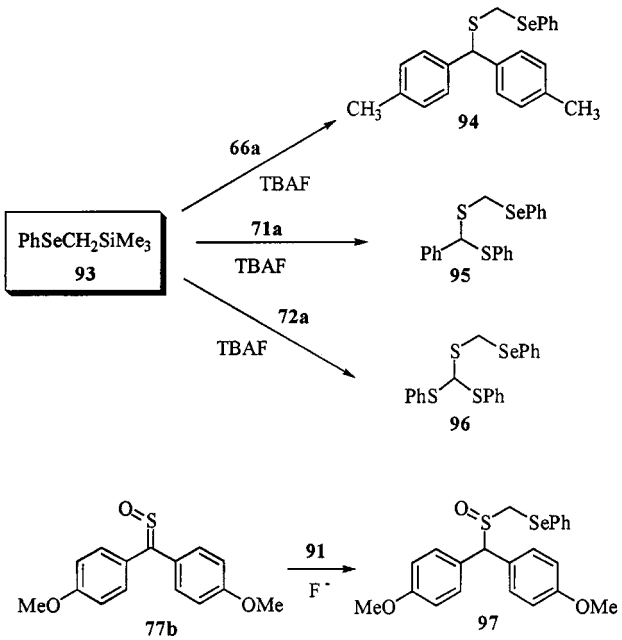
Reactions of the seleno compound **93** with sulfines afford phenylselenomethyl sulfoxides **97**, in which a sulfur atom is selectively oxidized in the presence of a selenium atom (Scheme 25).[84]

Furthermore, α-difunctionalized silyl nucleophiles, such as 2-trimethylsilyl-1,3-dithiane **(98)**, can also be used. These transfer the dithiane moiety onto different C=S groups, thereby affording the adducts **99** and **100**, which are again the products of a regiospecific thiophilic addition (Scheme 26).[84]

A different pathway has been observed employing other α-difunctionalized silylated nucleophiles. Thus, reactions of 1-trimethylsilyl-1-phenylthioethane **101a** and phenyl(phenylthio)trimethylsilylmethane **(101b)** with di-*p*-meth-

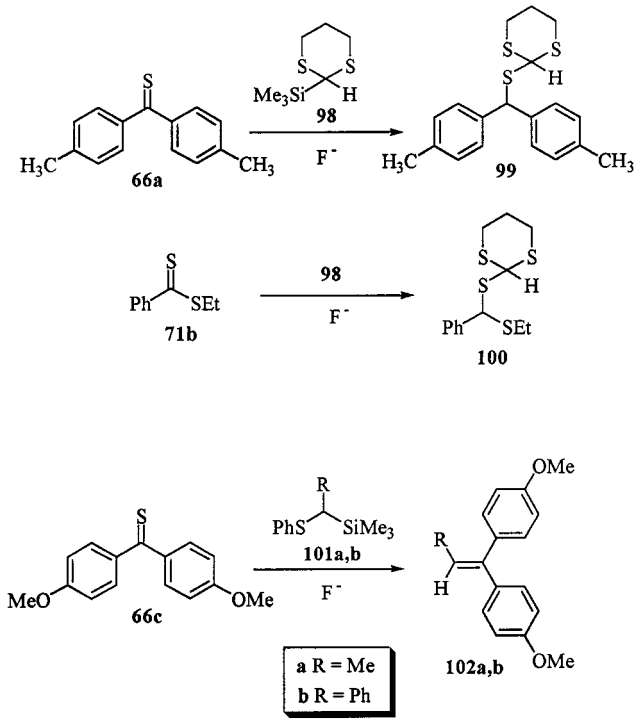


Scheme 24. Thiophilic addition of (phenylthiomethyl)trimethylsilane: synthesis of dithioacels and dithioacetal monoxides



Scheme 25. Thiocarbonyl functionalization with (phenylselenomethyl)trimethylsilane: synthesis of mixed selenothioacetals

oxythiobenzophenone **(66c)** furnished the trisubstituted alkenes **102a**,**b** in rather good yields (Scheme 26).[85] The mechanistic pathway of this last reaction is still unclear, al-



Scheme 26. Reactivity of α-disubstituted thiosilanes with thiocarbonyl compounds

though investigations aimed at its elucidation are currently underway.

Conclusions

Organothiosilanes are useful synthetic intermediates, participating in a constantly growing number of synthetic applications. The chemical behaviour of such compounds is dependent on the structure of the silyl sulfide itself, leading either to regiospecific selective delivery of sulfurated moieties or direct thionation.

Thus, for instance, reactions of aromatic and aliphatic silyl sulfides can lead, through a careful selection of the reaction conditions, either to regiospecific functionalization of α,β-unsaturated carbonyl compounds or to the synthesis of vinyl sulfides, through a clean transfer of the RS moiety.

On the other hand, the reactivity of the bis(silyl) sulfide HMDST proves rather peculiar, affording direct thionation of carbonyl-containing compounds, thus leading to a general and mild methodology for the generation of thioaldehydes and thioketones.

The versatility of this protocol is evidenced by its applications to the synthesis also of functionalized thioaldehydes, which can lead, through a fine tuning of the HMDST reactivity to *o*-azido thioaldehydes, fused isothiazoles, *o*-amino aldehydes and *o*-amino thioaldehydes.

Moreover, reactions of silyl nucleophiles with various thiocarbonyl derivatives are shown to be regiospecific, leading to direct thiophilic functionalization of the C=S moiety.

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