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REVIEW

Silylation–desilylation of quinones and their derivatives

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The silylation of quinones and their substituted derivatives for the protection of the reactive quinonic moiety and/or reactive substituents (in particular hydroxyl groups) is discussed in view of the wide applicability of the reaction for synthetic, biological and analytical purposes. Furthermore, the most common and efficient methods for the subsequent desilylation of the silylated quinones and their derivatives to the parent quinones or to the corresponding hydroquinones are discussed. Copyright © 2001 John Wiley & Sons, Ltd.

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1 INTRODUCTION

Quinones play a variety of roles in our overall life cycle, and interest in their biological function has stimulated basic chemical research in several areas. Quinones came to man's attention in two ways: as pigments and drugs.

In particular, hydroxyquinones, their substituted derivatives and their transition metal chelates have long been known to possess numerous chemically and biologically significant properties.[1–6] For instance, several of the best known and widely used anthracycline and tetracycline antibiotics possess the hydroxyquinone structure, which is thought to be responsible for their biological activity.[7,8]

Since the introduction of trimethylsilyl (TMS) ethers in the early 1970s for the protection of hydroxy groups,[9] the use of organosilicon reagents, as protective groups, has undergone substantial development. It is fair to say that, to date, in any relevant synthesis of reasonable complexity, the use of an organosilicon reagent of some kind is unavoidable. Experience shows that the critical parameters, for choosing the successful protecting group for a functional group from a wide range of choices, are generally the stability and the ease of cleavage of the blocking group rather than its introduction. Silyl protecting groups can be cleaved by treatment with fluoride ions under conditions that affect nearly no other functionalities.[10,11] They thus play an essential role in protecting group chemistry. A major factor contributing to the wide acceptance of silyl blocking groups is that both blocking and deblocking reactions are high yield and often quantitative reactions. The great interest in the use of organosilicon reagents as protecting groups in organic synthesis has resulted in many reviews and books, which provide surveys of publications and/or discuss particular aspects of the reaction,[12–17] such as selectivity, degree of reactivity for less reactive substrates, stability of the blocked substrate, etc.

Furthermore, numerous organosilicon compounds have been shown to possess potent biological activity.[18] Silyl derivatives of the well-known bioactive hydroxyquinones[19,20] are also expected to be highly bioactive.[2,3,7,8,21]

The silylation reactions of quinones with trialkylsilyl groups are of great importance for synthetic, analytical and biological purposes for the protection of the reactive quinonic moiety in a wide range of naturally occurring and biologically important macromolecules. The protection of the highly reactive hydroquinone function as a silyl ether, against destructive conditions, during multi-

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stage syntheses of several quinonoid compounds, followed by synthetic elaboration and oxidation, is an important synthetic strategy for the preparation of complex quinones. These series of reactions are particularly useful and are a common procedure in the synthesis of naturally occurring quinones, such as ubiquinone[22] and anthracycline antibiotics exhibiting high antitumor activity[23] as well as other man-made quinonic products.[24] Moreover, owing to the enhanced hydrolytic stability[25] of some silyl ethers, e.g. *tert*-butyl ethers, they could be submitted to pharmacological studies as lipophilic[20] derivatives of biologically active hydroxyquinones.

In particular, the TMS group has been used for the derivatization of quinonic compounds to be subjected to gas chromatography (GC) and GC mass spectrometry (MS) analysis,[26,27] prior to use as a protecting group. The purpose of trimethylsilylation is to reduce the polarity and the hydrogen bonding of the compound and to increase its volatility and thermal stability. These advantages make silylation an important tool for GC and GC/MS analysis of quinones.

The present review is concerned with the silylation–desilylation reactions of quinones and their substituted derivatives (mainly hydroxy derivatives) for the protection–deprotection of quinonic and/or hydroxyl reactive groups for synthetic, biological or analytical purposes. Conditions of protection and deprotection are described.

2 SILYLATION

The quinonoid nucleus embodies the potential of being a highly useful structural building block in organic synthesis. The major problems associated mainly with executing carbon–carbon bond-forming reactions on either quinones or hydroquinones lie with the generally high reactivity of these species with nucleophiles or electrophiles respectively.

2.1 Reversible protection of quinone carbonyl groups

Evans *et al.*,[28] in 1973, reported the first general method for reversibly protecting quinone carbonyl groups under exceedingly mild conditions, the blocking operation being effected with trimethylsilyl cyanide (TMSCN). The silylation reaction takes place in the presence of a catalytic amount of potassium cyanide/18-crown-6 complex under anhydrous conditions.[29,30] The products, *o*-TMS cyanohydrins (**a**), are particularly useful for the monoprotection of *p*-quinones, because they allow the functionalization of the remaining unprotected carbonyl group, e.g. by addition of organometallic reagents (**b**) (Fig. 1). This carbonyl derivatization method should amplify the utility of quinones as electrophilic substrates in organic synthesis. The silylation reaction was studied in a variety of substituted *p*-benzo- and *p*-naptho-quinones. It is particularly noteworthy that, with unsymmetrical quinones, the site of cyanosilylation is dictated by the relative carbonyl electrophilicity, and only in extreme cases, e.g. in the presence of *tert*-butyl substituents do steric effects become important.

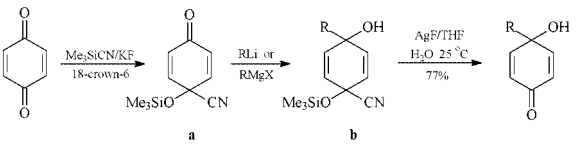

Figure 1 Protective silylation of *p*-benzoquinone with TMSCN.

The wide utility of this method is limited by the hydrolytic instability of the TMS group and, generally, from its sensitivity towards nucleophilic attack.[31–33]

The reformation of the carbonyl groups of *p*-quinols, from the protected forms, can usually be achieved in dilute aqueous acid or base and with fluoride ions, e.g. AgF[34,35] in aqueous THF at 25 °C.

The addition of *in situ* prepared Me_3SiCN to benzoquinone[33] gave a mixture of the mono- (21%) and di-cyanotrimethylsilyl ethers (63%) of benzoquinone, as well as bis(trimethylsiloxy-)-benzene (16%).

An example of regiospecific protection of a quinone carbonyl group was achieved by treatment of 2,6-dibromo-1,4-benzoquinone with TMSCN and a catalytic amount of triphenylphosphine in acetonitrile at 0 °C to give **a** uncontaminated by the isomer **b** (Fig. 2).[31] A change in solvent or increased reaction temperature resulted in a loss of regioselectivity. Furthermore, when **a** was treated with triphenylphosphine in acetonitrile at 40 °C for 240 h, isomerization to **b** occurred (Fig. 2).

As a consequence of the excellent regioselectivity that has been observed in the addition of TMSCN to unsymmetrically substituted *p*-qui-

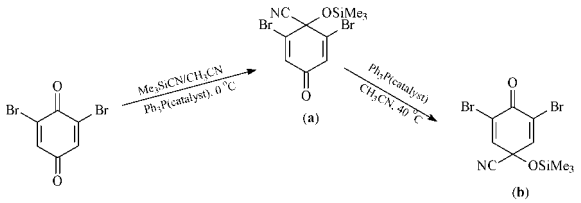

Figure 2 Regiospecific silylation of substituted *p*-benzoquinone with TMSCN.

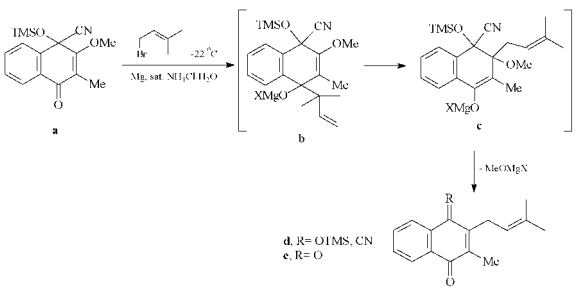

Figure 3 Regioselective silylation of unsymmetrically substituted *p*-quinones.

nones,[28] a variety of *p*-allyl quinols **b** are accessible (Fig. 3), which undergo allylic rearrangement **c** in a predictable fashion leading to unsymmetrically prenylated quinones as vitamin K_2 **e** by deblocking the appropriate silylated intermediate allyl-quinone **d** with AgF under standard conditions[28,32] (Fig. 3).

An interesting silicon-containing compound has been prepared from benzoquinone with sodium-bis-trimethylsilyl-amide in the presence of Me_3SiCl in C_6H_6 to give *N*,*N*′-bis-trimethylsilyl-*p*-benzoquinonediimide.[36] The product is very reactive (light, air and moisture), but can be purified by sublimation (Fig. 4).

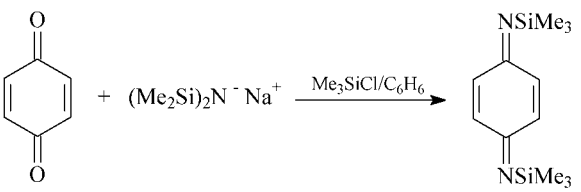

Figure 4 Silylation of *p*-benzoquinone with sodium-bis-trimethylsilyl amide.

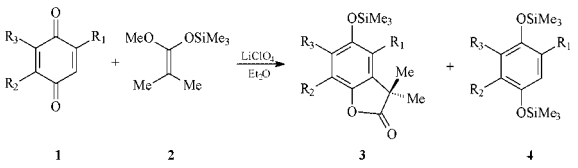

Figure 5 Addition of *o*-silylated ketene acetal to quinone.

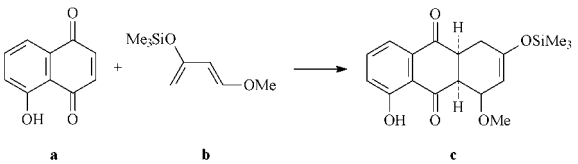

Figure 6 Diels–Alder cycloaddition reaction of juglone with silylated diene.

In 1992, Ipaktschi and Heydari[37] reported the 1,4-conjugative addition of *o*-silylated ketene acetals to quinones in the presence of lithium perchlorate in ether to form 2(3*H*)-benzofuranones **a** and the corresponding hydroquinone silyl ethers **b** (Fig. 5).

Diels–Alder reactions of 5-hydroxy-1,4-naptho-quinone (juglone) and its derivatives[38–42] have played an important role in the synthesis of quinonoid natural products and their relatives. Not surprisingly, therefore, much attention has been devoted to controlling the *regio*- and stereochemical outcome of such cycloaddition reactions (Fig. 6).

Polycyclic aromatic hydrocarbons (PAHs) in water ice were exposed to ultraviolet (UV) radiation under astrophysical conditions, and the products were analyzed by IR and MS. Peripheral carbon atoms were oxidized, producing partially hydrogenated aromatic alcohols, quinones[43] and ethers.

2.2 Reductive silylation of quinones

The reductive silylation of quinones has attracted much attention, and several reports have appeared, because it offers the possibility of protecting the quinonic fragment as well as that of the correspond-

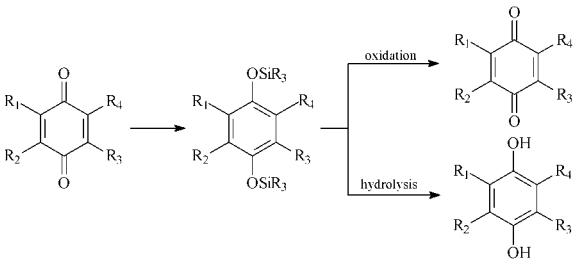

Figure 7 Reductive silylation and subsequent deprotection or hydrolysis of *p*-benzoquinones.

ing hydroquinone in a wide range of naturally occurring and biologically important macromolecules. The silylated products, regarding the desilylation method, can be converted easily by oxidative desilylation to their parent quinones[28,44–46] or readily hydrolyzed to the corresponding hydroquinone as described in Fig. 7. In addition, silicon-based reducing agents have attracted a great deal of attention recently because of their low toxicity compared with the corresponding tin-based reagents.[47–49]

In 1968, Becker[50] studied the reductive silylation of 3,3′,4,4′-tetra(*tert*-butyl)phenoquinone and 3,5-bis(*tert*-butyl)phouxone with diphenyl-, triphenyl-, and tribenzyl-silane at high temperatures (300–350 °C) in goods yields (60–80%), as shown in Fig. 8.

In 1970, Bouas-Laurent *et al.*[51] reported the reductive silylation of several *p*-quinones with Me_3SiCl/ Mg in THF to the corresponding 1,4-bis(trimethylsiloxy)arenes in 30–94% yields.

Neumann and Neumann[52] and Beaumont *et al.*[53]

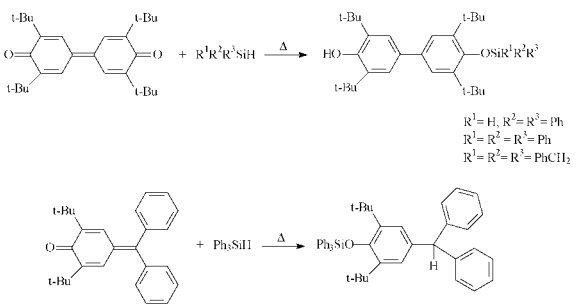

Figure 8 Reductive silylation of phenoquinone and phouxone with aryl silanes.

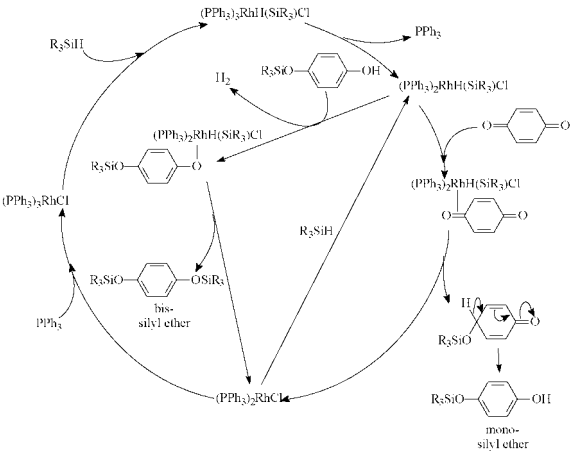

Figure 9 Catalytic cycle of reductive silylation of *p*-benzoquinone with Wilkinson's catalyst.

in 1970, almost simultaneously, announced the reductive silylation of *p*-quinones with bis(trimethylsilyl)mercury $(Me_3Si)_2Hg$ to bis(*o*-silyl)arenes (44–63%). The reaction takes place with 1,2- and 1,4-napthoquinone, as well as with simple ketones such as acetone and cyclohexanone. The yields for the quinone are quite satisfactory. Some evidence is presented for a radical intermediate,[53] but the possibility of a molecular reaction leading directly to product is also presented.

Further, Neumann and Neumann[54] in 1972 and later, in 1980, Adeleke and Wan[55] used bis(trimethylsilyl)mercury for the reductive silylation of the parent quinones 1,4-benzoquinone, 1,4-naphthoquinone and 9,10-anthraquinone with a free radical mechanism.

Also, Tsutsumi and coworkers treated *p*-benzoquinone with Me_3SiCl/K to obtain the silylated product in 28% yield. These conventional silylations are generally accompanied by the concurrent formation of a large amount of inorganic salts.[56]

The utility of reductive silylation led Snyder and Rapopport[45] and later Matsumoto *et al.*,[46] to explore a newer type of reaction, reporting the effective silylation of *p*-quinones with *in situ* prepared trimethylsilyl iodide (TMSI), from hexamethyldisilane in the presence of a catalytic amount of iodine, under mild conditions, to 1,4-bis(trimethylsiloxy)arenes in high yields.

Moreover, Kumada and coworkers[57] and Rapopport and coworkers[45] have reported that 1,2-difluorotetramethyldisilane reacted at 100 °C with

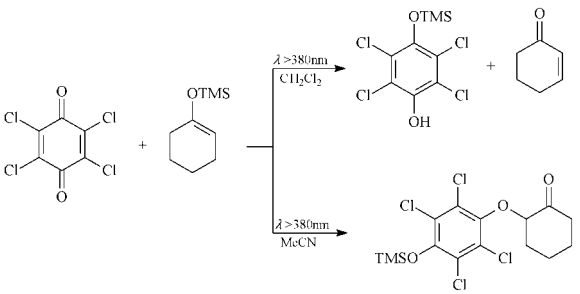

Figure 10 TMS group transfer to tetrachloro-*p*-benzoquinone.

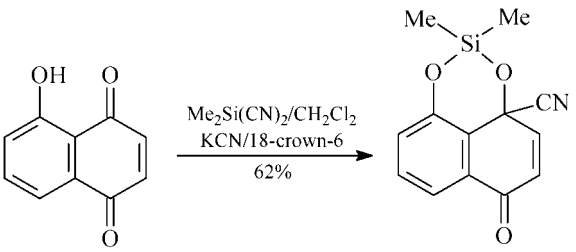

Figure 12 Regiospecific protection of juglone with $Me_2Si(CN)_2$.

p-benzoquinone, in the presence of a palladium catalyst, to afford the bis(silyl)benzene in 41% yield.

In 1978, Miller and Stewart[58] reported the direct preparation of halohydroquinones and their silyl ethers.[58]

According to the unpublished results of Naruya and Maruyama cited in Refs 1, 23, trimethylsilyl trifluoromethanesulfonate (TMSOTf) ester is equally efficient for the reductive silylation of quinones in the presence of 2,6-loutidine.

Bakola-Christianopoulou[44] reported the reductive hydrosilylation of quinones by 1:1 stoichiometric addition of Et_3SiH in the presence of Wilkinson's catalyst [$(Ph_3P)_3RhCl$]. The same reaction using excess of Et_3SiH yielded the corresponding bis-silyl ethers,[59] providing an easy method for protecting the highly reactive quinonic groups of naturally occurring macromolecules and other compounds of high biological importance. The resulted bis-silyl ethers readily undergo oxidative desilylation or acid hydrolysis to give the parent quinones and the corresponding hydroquinone derivatives respectively (Fig. 9).

Bockmann *et al.*[60] studied the direct transfer of the TMS group upon dehydrosilylation–hydrosilylation, according to Fig. 10, by the formation of the tetrachlorohydroquinone solely as the mono-trimethylsilyl ether **a**. Time-resolved (picosecond) spectroscopy identifies the critical role of solvent polarity in modulating the ion-pair dynamics of the reactive intermediate [CTE^+, CA^-] from the photoinduced electron transfer of cyclohexanone enol trimethylsilyl ether (CTE) and chloranil (CA) to yield selectively the dehydrosilylated enone **b** in CH_2Cl_2, but the oxidative adduct **c** in CH_3CN. Furthermore, solvent polarity and added salts play a major role[61] in establishing the product distribution between **b** and **c** and modulate the ion-pair behavior *via* the 'special salt effect'[62] to divert the enone pathway to adduct formation.

Finally, silyltellurides serve as new silicon-based chemoselective reducing agents and reduce quinones to the corresponding bis-silylated hydroquinones.[63] The reaction proceeds under ambient thermal conditions without the need of any additional promoters or catalysts and gives the products in excellent yields. Several control experiments suggest that the reductive bis-silylation reaction is initiated by a single electron transfer mechanism from silyltellurides to quinones, as depicted in Fig. 11.

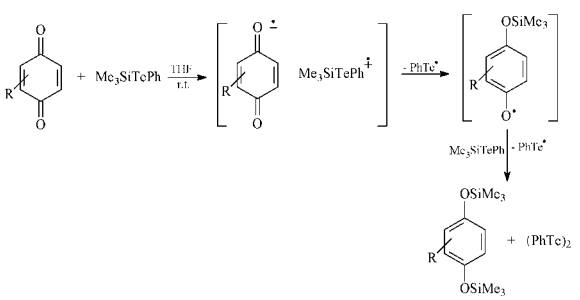

Figure 11 Reductive silylation of *p*-benzoquinone with silyltellurides.

2.3 Silylation of hydroxy derivatives of quinones

The silylation of hydroxy derivatives of quinones has also attracted much attention, because it offers the possibility of protecting the functional carbonyl and hydroxyl groups against destructive reaction

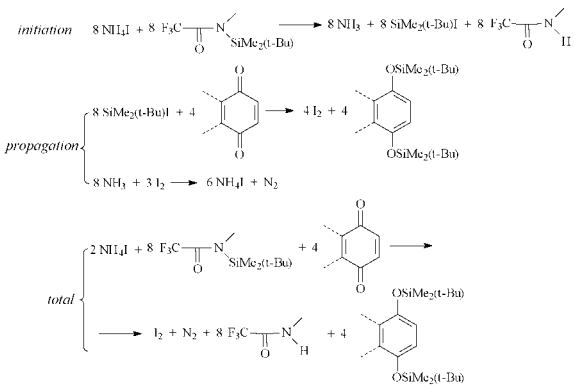

Figure 13 Proposed mechanism for the silylation of hydroxynaphthoquinones with MTBSTFA.

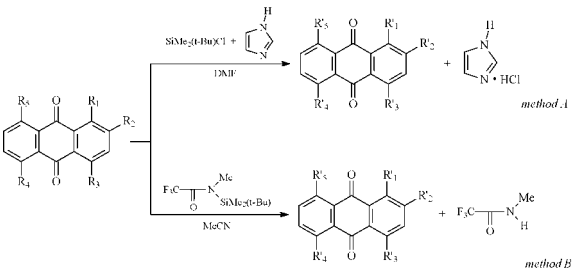

Figure 14 Procedures for the partial silylation of hydroxyquinones.

conditions in a synthetic process, thus providing suitable intermediates. The products may also be used as prodrugs, as their lipophilicity coupled with the facile hydrolysis of the Si—O bond would allow them to penetrate easily through lipophilic membranes and liberate the parent drug by gradual hydrolysis. Moreover, the formation of volatile, non-polar hydroxyquinone silyl derivatives has become essential for their GC or GC/MS analysis.

Regiospecific protection of 5-hydroxy-1,4-napthalenedione (juglone) was achieved by the use of Me_2SiCN_2 in the presence of catalytic amounts of the complex KCN/18-crown-6 to give six-membered rings. The cyanosilylated derivative was desilylated by treatment with MeOH or AgF in THF.[1,64] This method can be used for the differentiation of one carbonyl group from the other (Fig. 12).

2.4 *tert*-Butyldimethylsilyl (TBDMS) ethers

The advantages of using silyl protecting groups in organic synthesis include the possibility of regulation of their hydrolytic stability by choosing suitable alkyl substituents for Si.[65–68]

So, since sterically crowded TBDMS ethers were found[25,69] to be much more stable to hydrolysis as intermediates in organic synthesis than the hydrolytically unstable TMS ethers, and are readily cleaved by a variety of selective conditions (fluoride ions or aqueous acid), they are now considered to be one of the most useful protective groups. Bakola-Christianopoulou and Apazidou[70,71] studied both the reductive *tert*-butyldimethylsilylation and the selective partial *tert*-butyldimethylsilylation of hydroxyquinones by complete masking of all the hydroxyl groups of hydroxyquinones, without affecting the carbonyl groups, since, despite the large amount of information about hydroxyquinones and their derivatives, few studies have been aimed at their partially silylated products.

Thus reductive silylation of a series of hydroxynapthoquinones with *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-1,1,1-trifluoroacetamide (MTBSTFA) in the presence of NH_4I afforded the TBDMS ethers of the corresponding hydroquinones (arenes silyl ethers) in nearly quantitative yields (Fig. 13).[70]

Partial silylation of hydroxyquinones, i.e. hydroxynaptho- and hydroxyanthra-quinones with MTBSTFA, *via* an intermediate pentacoordinated silicon species[70] (for synthetic purposes, since hydroxyquinones are synthetic intermediates of great importance) has been reported. In the case of hydroxyanthraquinones the silylation has been applied in two ways: *tert*-butyldimethylsilylchloride (TBDMSC1) and MTBSTFA were each used as a silylating agent, under optimized reaction conditions, in two different silylating procedures (A and B), each one with its own advantages of simplicity, efficacy and shortness (Fig. 14).[71]

2.5 GC/MS analysis of hydroxyquinones silyl derivatives

Combined GC/MS techniques are widely applied in biochemistry, natural products, environmental, agricultural and technical chemistry to identify and analyze quinones. The well-documented fragmentation pattern of quinones facilitates the assign-

ment of chromatographic peaks when the mass spectrometer is used as a specific detector.[72]

The parallel presence of carbonyl and hydroxyl groups in hydroxyquinone molecules results in the appearance of strong inter- and intra-molecular hydrogen bonding, which increases further the polarity of the hydroxyquinones and reduces their volatility. The conversion into their less polar and more volatile and thermally stable silyl ethers improves their utility for GC/MS analysis and identification. Hence GC/MS study of hydroxyquinones, both naturally occuring and synthetic, is of importance.

Since their introduction by Luukkainen *et al.*[73] TMS ethers have been widely used in the gas-phase analysis of various classes of organic compounds, as well as in quinone derivatization.[74]

The separation and identification of 37 naturally occurring hydroxyanthraquinones as the corresponding TMS derivatives by GC/MS analysis has been described.[75] Hendriksen and Kjosen[76] dealt with the reductive silylation of some hydroxyanthraquinones for GC/MS analysis. Their approach suggests prolonged reaction periods and complex reaction conditions, involving both bases and solvents.

Bakola-Christianopoulou *et al.*[77] recently reported a successful application of GC/MS to the study of the progress of the reductive (in the sense of complete silylation of all the functional groups of the molecule, e.g. all hydroxyls and carbonyls) silylation of hydroxyquinones as well as to their separation and characterization in mixtures. They reported a simple method for the quantitative reductive silylation of both hydroxynaptho- and hydroxyanthraquinones with TMSI, prepared *in situ* by the catalytic action of ammonium iodide to *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA), the most volatile TMS-amide. They also reported a detailed discussion of the mass spectra of the silylated products and a proposal for a fragmentation mechanism. The fragmentation patterns of the silylated compounds provided valuable information and some useful rules for the interpretation of their structure and, consequently, about the structure of the initial isomer hydroxyquinones. The silylation scheme was also applied to synthetic mixtures of hydroxyquinones, resulting in successful GC/MS separation of all the ingredients (silylated derivatives), which is particularly important for the isomers of hydroxyquinones. GC/MS also proved to be an effective method for the optimization of the silylation reaction conditions. In addition, this reductive silylation procedure was

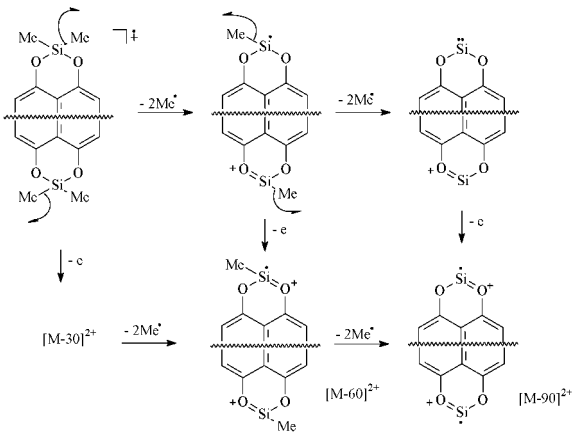

Figure 15 MS fragmentation pattern of silylated hydroxyquinones.

applied successfully for the complete GC-selected ion monitoring (SIM) MS separation and identification of 19 steroids in urine samples as their pertrimethylsilyl ethers, with well-formed peak shapes due to their increased relative retention times (RRTs) and highly diagnostic MS features.[78]

2.5.1 Selective partial silylation for GC analysis

Despite the extensive studies of hydroxyquinones and their derivatives, little information is available about the selective partial silylation (of only the hydroxyl groups) for GC analysis.

Partial silylation of hydroxyanthraquinones for GC[74,79] or for GC/MS analysis[75,80] has been reported without fully describing the mass spectra features.

Furthermore, partial silylation of hydroxyquinones, i.e. hydroxynaptho- and hydroxyanthraquinones, with MTBSTFA, for GC/MS analysis of their mixtures, in case it cannot be carried out, because the molecular ions are beyond the range (10–800 amu) of the low-cost quadrupole mass spectrometers, has been reported.[70,71] MTBSTFA proved to be a powerful silylating agent because increased molecular weights of the derivatives (over the corresponding TMS) result in increased retention times and may increase resolution. In addition, increased molecular weights lead to an increase in sensitivity with the flame ionization detector. When silylation reagents are consumed in the hydrogen flame, silicon dioxide (SiO_2) is formed. MTBSTFA contains three fluorine atoms,

which form HF in the detector flame and react with the SiO_2 to form volatile products. Derivatives also have excellent GC properties and also produce simpler, more easily interpreted mass spectra.

Moreover, partial silylation of hydroxyquinones is also reported[81] to be carried out in a simple, one step, quantitative manner, using MSTFA as both silylating agent and solvent under conditions optimized accordingly. The silylated products were studied by GC/MS. A detailed study of their mass spectra revealed the governing features of the fragmentation patterns and helped in the establishment of useful rules of thumb for the deduction of the hydroxy-group position in the unknown hydroxyquinone backbone. Moreover, doubly charged ions reveal the presence of two hydroxyl groups in *ortho* or *peri* position to the *para* carbonyl groups of the hydroxyquinone molecule (Fig. 15).

In addition, this partial silylation method was successfully applied to the GC/MS analysis of a mixture of nine bile acids.[82]

In conclusion, to our knowledge, the well known silylation methods for hydroxyquinones, that have been applied for the GC or GC/MS analysis of their mixtures are as follows:

(A) For the selective partial silylation of only their hydroxyl groups

- a mixture of $TMSCl/Me_3SiNHSiMe_3$ in the presence of pyridine in the ratio 1:5 without heating[74] and 1:2 with heating at 80 °C[76]
- bis-trimethylsilylacetamide (BSA) in $CHCl_3$ without heating in $CHCl_3$[79]
- a mixture of BSA/trimethylsilylchloride (TMSCl) in the ratio 5:1 without heating[80]

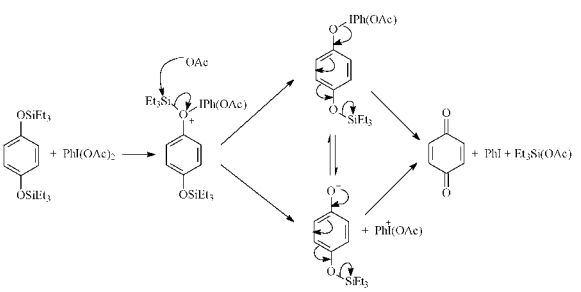

Figure 16 Proposed mechanism for the oxidative desilylation of bis(triethylsilyl)ethers of hydroquinones.

- a mixture of BSA/trimethylsilylimidazole (TMSIM)/TMSCl in the ratio 3:3:2[75]
- MSTFA[81]

(B) for the reductive silylation of all hydroxyl and carbonyl groups

- a mixture of $TMSCl/Me_3SiNHSiMe_3$ in the ratio 1:2, in CH_2Cl_2, in the presence of a catalytic amount of zinc and heating at 80 °C in good yields[76]
- a mixture of $MSTFA/NH_4I$ for the *in situ* formation of TMSI.[77]

3 DESILYLATION

3.1 Oxydative desilylation of silylated derivatives to the parent quinones

Even though a wide range of oxidants has been utilized for the oxidative desilylation of the silylated quinones to the parent quinones, the high acidity required precludes their use with substrates containing acid-labile groups.[83–86]

So far, oxidation of bis-TMS and TBDMS ethers of a series of substituted *p*-hydrobenzoquinones to the parent substituted *p*-benzoquinones has been achieved, in high yields, with pyridinium chlorochromate (PCC) in CH_2Cl_2,[87] as well as with chlorochromate trimethylsilyl ether ($ClCrO_3SiMe_3$) in CH_2Cl_2.[88] Deprotection with hydrate $FeCl_3/SiO_2$ in CH_2Cl_2, in good yields has been achieved only in the case of bis-substituted derivatives of the bis-TBDMS ether of the hydrobenzoquinone,[89] whereas, finally, anodic oxidation with MeOH, even though rarely applied, leads to the corresponding parent quinones with good results,[90] in particular in the case of poly-substituted silyl ethers of hydroquinones.

The bis(triethylsilyl)ethers of hydroquinones are found to undergo oxidative desilylation readily[59] upon their reaction with (diacetoxyiodo-)benzene (DIB), in CH_2Cl_2 and give good yields (70%). A proposed mechanism is presented in Fig. 16.

In addition,[91] phenols with a weakly acidic character can be converted directly into quinones.[91b]

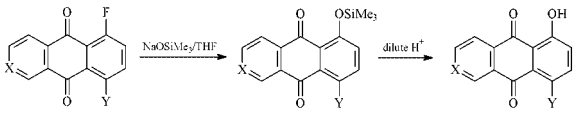

Figure 17 Substitution of F by OH in substituted quinones through the acidolysis of the intermediate silylated derivative.

3.2 Hydrolysis of silylated derivatives to hydroquinones

Concerning the hydrolysis of silylated derivatives to hydroquinones, the variation of the substituents on silicon allows modification of their stability towards acids and bases, as well as the selectivity of the cleavage with fluoride ions.[92] Generally, the relative rates (k_{ret}^{-1}) of acidolysis or basic solvolysis for a series of silyl ethers of type R—O—SiR′$_3$, are as follows:

Acidolysis ($\mathbf{R'_3Si}$)

$$Me_3Si\ (1) < Et_3Si(64) < t\text{-}BuMe_2Si(20\,000) < i\text{-}Pr_3Si(700\,000) < t\text{-}BuPh_2Si(5\,000\,000)$$

Basic solvolysis ($\mathbf{R_3Si}$)

$$Me_3Si\ (1) < Et_3Si(10\text{–}100) < t\text{-}BuMe_2Si \approx t\text{-}BuPh_2Si(20\,000) < i\text{-}Pr_3Si(100\,000)$$

As a consequence of this range of hydrolysis, silyl ethers with modulated solvolytic action are now commonly used in synthesis.

3.3 Fluoride-based reagents

It is a general perception that fluoride-based reagents, e.g. $BF_3{\cdot}OEt_2$, HF/NaF, CsF, KF, *n*-Bu_4NF (TBAF),[8,25,93–95] etc., are the best choice of reagents for cleaving silyl ethers[96–100] under conditions that affect nearly no other functionalities. Of the known fluoride-based reagents, TBAF in tetrahydrofuran (THF) and KF have a selectivity in the desilylation of phenolic or diphenolic silyl ethers.[101–103] Although there is a series of methods known for the deprotection of aliphatic silyl ethers,[98] to our knowledge only a few methods have been reported for the demasking of TBDMS phenolic ethers. Treatment of these *tert*-butyldimethylsilyl ethers with KF in the presence of catalytic amounts of HBr in dimethylformamide[102] generates the corresponding phenols or diphenols in high yields under conditions mild enough even for the regeneration of a base-sensitive phenol. Hydrobromic acid is an effective catalyst both in terms of equivalents of catalyst and of time required for completion of the reaction. Parlowa *et al.*[103] recently reported a mixed resin bed for the quenching and purification of desilylating reactions involving tetrabutylammonium fluoride as the reagent.

3.4 Acidolysis

Of particular interest is the development by Krapcho and Waterhouse[104] of a direct method for the introduction of a hydroxyl group on the readily available fluoro-substituted anthracene-9,10-diones and related aza analogues. Treatment of fluoro-9,10-anthracene-dione (fluoro-anthraquinone) with sodium trimethylsilanoate in THF *via* S_NAr ipso substitution, followed by acidification, leads to the corresponding hydroxyl analogues (Fig. 17).

Triethylsilylethers of various quinones undergo acid hydrolysis in aqueous methanol to give the corresponding hydroquinones.[59,105]

tert-Butyldimethylsilyl ethers of phenols and alcohols are desilylated to the parent phenols and alcohols in dimethylsulfoxide, at 80 °C, in the presence of 0.2–0.4 equivalents of $P(MeNCH_2CH_2)_3N$.[106]

In 2000, Curini *et al.*[107] reported an easy solid-state method for cleavage of sterically hindered phenolic silyl ethers in good to excellent yields using a new heterogeneous catalyst [Zr $(KPO_4)_2$].

3.5 Selective desilylation of TBDMS ethers

The selective desilylations of TBDMS ethers[108] of phenols and alcohols have been achieved using TBAF and HF respectively.[93] These deprotection reagents cannot be applied to selective desilylation of TMS ethers because the latter are much more readily hydrolyzed, regardless of their phenolic or alcoholic nature. Recently, Hunter *et al.*[109] reported on the chemoselectivity and mechanism of desilylation of TBDMS ethers with TMSOTf.

Among the systematically studied reagents to effect selective removal of silyl groups from silylated phenols are reported to be KF/18-crown-6,[110] K_2CO_3/Kryptofix 222,[111a] K_2CO_3/aqueous EtOH,[111b] Dowex 1-X8 (OH-form)[112] and 37% KF/basic-alumina with ultrasound.[113] Other methods using TBAF have been reported as parts of total syntheses.[114–117] Recently, in 1999, Crouch *et al.*[118] reported the selective deprotection of aryl

silyl ethers to phenols, in the presence of silyl protected alcohols, in good to excellent yields, using a biphasic system of ten equivalents of NaOH and catalytic Bu_4NHSO_4 in 1,4-dioxane. Neutral alumina in a microwave[119] and 5 mol% $PdCl_2(CH_3CN)_2$ in refluxing acetone[120] have a selectivity in the desilylation of phenolic silyl-ethers.

Treatment of trialkylsilyl ethers with cerium(III) chloride heptahydrate[121] and sodium iodide in acetonitrile, under very mild conditions, provides a simple and chemoselective process for desilylation, and the parent alcohol was obtained in high yield. The trialkylsilyl ethers have been cleaved selectively in the presence of acetate, benzyl and tetrahydropyranyl ethers. Finally, Lee *et al.*[122] announced in 1998 a novel, highly efficient and selective desilylating method for trialkylsilyl ethers to their corresponding alcohols in CBr_4/CH_3OH (0.1 equalents/10 ml) as a reaction system under refluxing conditions.

3.6 Hydroxyquinone TBDMS ethers

Desilylation of a series of hydrolytically stable hydroxyquinone TBDMS ethers to the corresponding biologically important hydroxyquinones[123] was achieved in three different desilylating procedures by the use of the powerful desilylating agent KF in the presence of catalytic amounts of aqueous 48% HBr, KF in basic Al_2O_3 and *n*-Bu_4NF. Each procedure has its own advantages of simplicity, efficacy, clarity and shortness.

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