Grignard Reagents and Silanes

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I. INTRODUCTION

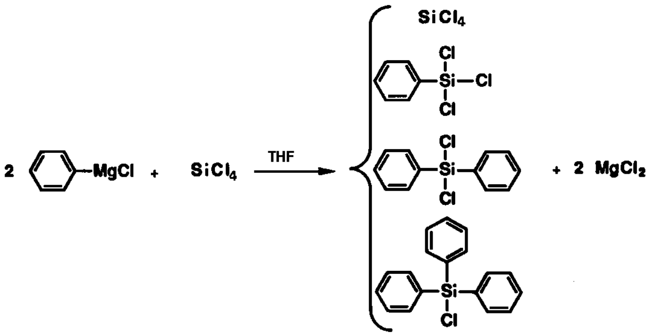
This review considers two aspects of the interaction of Grignards with silanes. First, focusing on technologies that are still viable within the context of current organosilane and silicone technology, guidelines are provided for silicon-carbon bond formation using Grignard chemistry. Second, the use of silane-blocking agents and their stability in the presence of Grignard reagents employed in organic synthesis is discussed.

II. FORMATION OF THE SILICON-CARBON BOND

A. Background

The genesis of current silane and silicone technology traces back to the Grignard reaction. The first practical synthesis of organosilanes was accomplished by F. Stanley Kipping in 1904 by the Grignard reaction for the formation of the silicon-carbon bond [1]. In an effort totaling 57 papers, he created the basis of modern organosilane chemistry. The development of silicones by Frank Hyde at Corning was based on the hydrolysis of Grignard-derived organosilanes [2]. Dow Corning, the largest manufacturer of silanes and silicones, was formed as a joint venture between Corning Glass, which had silicone product technology, and Dow, which had magnesium and Grignard technology, during World War II. In excess of 10,000 silicon compounds have been synthesized by Grignard reactions. Ironically, despite the versatility of Grignard chemistry for the formation of silicon-carbon bonds, its use in current silane and silicone technology has been supplanted by more efficient and selective processes for the formation of the silicon-carbon bond, notably by the direct process and hydrosilylation reactions. The intention of this review is to indicate where the Grignard reaction remains a viable technology for the preparation of silanes.

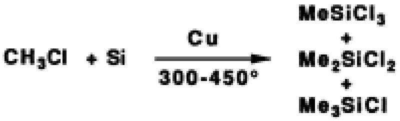
The generalized structure of an organosilane is $R_nSiX_{(4-n)}$, where X is an electron-withdrawing group, typically halide. In the simplest and earliest examples of the reaction chemistry, silicon tetrachloride was substituted by addition of Grignard reagents, such as ethylmagnesium bromide and phenylmagnesium chloride [1,3]. In addition, Grignard reagents substitute alkoxides (OR), siloxanes (O-Si), and nitriles (CN).



(1)

The general inability to accomplish clean, integral, partial substitution leading to organohalosilanes is the primary, but not the only, restriction of the Grignard process. The difficult separation of the corrosive, hydrolytically sensitive halosilanes from the reaction mixture, the relatively low product concentration, and the complex technology involved in removal of by-products, and the recycle of solvents pose significant design barriers in process scale-up and result in economic barriers for product acceptance [4]. If the target compound is tetraalkylsilane or equivalent, process control is not as critical, and water workup is allowed. Water workup is often facilitated by the addition of dilute hydrochloric acid, particularly when products are derived from alkoxysilanes.

Alternative technologies that are used to generate organosilanes on a commercial scale are the Rochow-Muller direct process, which works best with low molecular weight alkyl and aryl halides [5]:



$$CH_3Cl + Si \xrightarrow[300\text{-}450°]{Cu} MeSiCl_3 + Me_2SiCl_2 + Me_3SiCl \qquad (2)$$

The hydrosilylation reaction, which is limited by the availability of hydridosilanes and olefins [6]:

$$RCH{=}CH_2 + HSiCl_3 \xrightarrow{Pt} RCH_2CH_2SiCl_3 \qquad (3)$$

The Barry process, which is generally limited by thermal stability of the aryl precursors [7,8]:

(4)

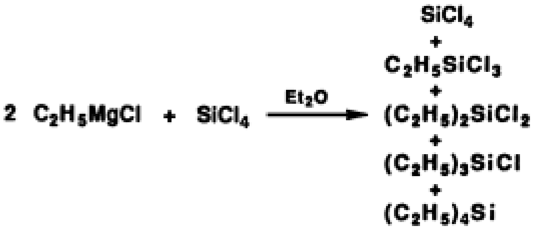
Although the production of organosilanes by non-Grignard processes is at least 1000 times greater than with Grignard processes, they remain essential for many of the specialty silanes. The versatility of the Grignard process allows the introduction of a broader range of functionalities than alternative technologies. The viability of the Grignard process in organosilane production depends on the degree to which problems of isolation and purification can be mitigated. Examples of silanes produced on a commercial basis (>2 tons/year) by Grignard technology are

Dialkyldialkoxysilanes	Silicone intermediates, polyolefin catalysis
Phenylalkoxysilanes	Silicone intermediates, polyolefin catalysis
Phenylmethylsiloxanes	Silicone intermediates, diffusion pump fluids
Diphenylmethylchlorosilane	Silicone and pharmaceutical intermediate
Chloromethyltrimethylsilane	Pharmaceutical intermediate
Triethylsilane	Pharmaceutical intermediate
Vinyltrimethylsilane	Polymer and pharmaceutical intermediate
Allyltrimethylsilane	Polymer and pharmaceutical intermediate

B. Reactivity Trends for Grignards and Silanes

The following general trends apply to the formation of organosilanes by Grignard methods.

1. Substitution is Rarely Stepwise



$$2\ C_2H_5MgCl + SiCl_4 \xrightarrow{Et_2O} SiCl_4 + C_2H_5SiCl_3 + (C_2H_5)_2SiCl_2 + (C_2H_5)_3SiCl + (C_2H_5)_4Si \quad (5)$$

Multiple substitution is usually slightly favored, presumably owing to the complex “dimeric” nature of the Grignard reagent. Furthermore, the activation energy for sequential substitution varies over only a narrow range as evidenced by the 18.5-21.2 kcal/mol range reported for the methylchlorosilanes [9].

2. Substitution Versus Halide

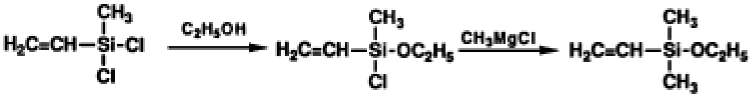
Si–F > Si–Cl > Si–Br > Si–I

Chlorosilanes are the only commercial intermediates employed. Fluorosilanes have interesting features in that they allow substitution by sterically hindered alkylmagnesium halides and, by utilization of weak HF of HF complexes, isolation can be conducted in aqueous regimes. Hexafluorosilicate salts are also substituted by Grignards, although the reaction appears to have little usefulness [10]. Bromosilanes react much slower than chlorosilenes. For example, complete substitution of tetrachlorosilane by methylmagnesium chloride, to form tetramethylsilane, is facile in diethyl ether at room temperature, whereas complete substitution of tetrabromosilane by methylmagnesium bromide requires pressure at 160°C [11].

3. Substitution Versus Electron-Withdrawing Group

Si–CN > Si–Cl > Si–OR > Si–O–Si

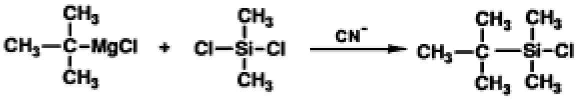
For the substitution reaction, the alkoxy group of the silane is practically limited to linear radicals, notably methoxy and ethoxy. Although substitution of chlorides accounts for most transformations, the conversion of chlorides to other electron-withdrawing groups provides the ability to alter the degree of substitution in reactions [12,13]. In some reactions, the relatively slow reaction of an alkoxy group relative to a chlorine is exploited. For example, the target compound divinyltetramethyldisiloxane, an important endcapper in silicone chemistry, cannot be prepared in practical yield by the addition of 1 Eq of methyl Grignard to vinylmethyldichlorosilane, followed by hydrolysis. Alternatively, mono-alkoxylation of vinylmethyldichlorosilane increases the selectivity for substitution by only 1 mol of Grignard. (This process is utilized only when availability of dimethylchlorosilane for the alternate route of hydrosilyation of acetylene does not meet demand.)



$$H_2C{=}CH{-}\overset{CH_3}{\underset{Cl}{Si}}{-}Cl \xrightarrow{C_2H_5OH} H_2C{=}CH{-}\overset{CH_3}{\underset{Cl}{Si}}{-}OC_2H_5 \xrightarrow{CH_3MgCl} H_2C{=}CH{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}OC_2H_5$$

(6)

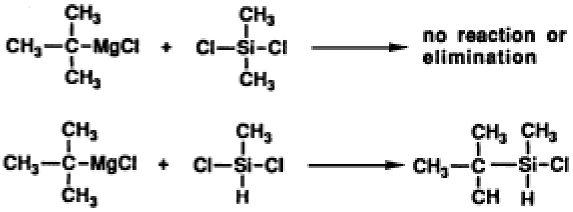
Control of substitution by partial alkoxylation is much less effective when an alkoxychlorosilane with a single organic substituent without steric bulk is involved. For methyldiisopropoxychlorosilane little selectivity between substitution of chloride versus isopropoxide was observed [14]. Although cyanosilanes are rarely used directly in Grignard reactions, the addition of 5 mol % of a cyanide salt often catalyzes Grignard substitution reactions [15-17]. Thiocyanate, another pseudohalogen, exerts a similar effect [18].



$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}MgCl + Cl{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}Cl \xrightarrow{CN^-} CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}Cl$$

(7)

4. The Introduction of Si–H Facilitates Substitution of Halides



$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}MgCl + Cl{-}\overset{CH_3}{\underset{CH_3}{Si}}{-}Cl \longrightarrow \text{no reaction or elimination}$$

$$CH_3{-}\overset{CH_3}{\underset{CH_3}{C}}{-}MgCl + Cl{-}\overset{CH_3}{\underset{H}{Si}}{-}Cl \longrightarrow CH_3{-}\overset{CH_3}{\underset{CH}{C}}{-}\overset{CH_3}{\underset{H}{Si}}{-}Cl$$

(8)

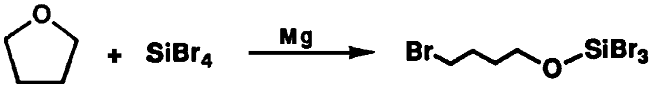
5. Reaction with Hydrides

Despite their relative basicity, Grignard reagents do not generally react with hydrides. However, in tetrahydrofuran at elevated temperature and in the case of polyhydridosilanes in diethyl ether, the hydride can also be displaced [19].

(9)

6. Tetrahydrofuran Versus Diethyl Ether as Solvent

Of the two most common solvents for Grignard reagents, substitution is more facile with tetrahydrofuran than diethyl ether. The ability to run reactions at more elevated temperatures owing to the higher boiling point of tetrahydrofuran allows substitution to proceed further in some sterically constrained systems. The use of tetrahydrofuran as a solvent has two distinct operational differences when compared with diethyl ether. Magnesium halides are relatively soluble in tetrahydrofuran, requiring a concentration or second-solvent precipitation to remove salts. Under certain reaction conditions, in particular the presence of activated magnesium metal, tetrahydrofuran undergoes a ring-opening reaction with bromosilanes and iodosilanes [20,21].



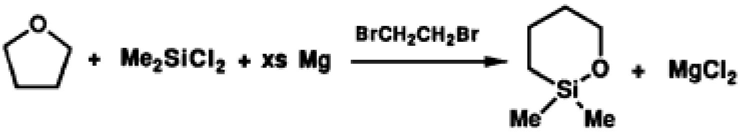
(10)

7. Halide Exchange Occurs Between Grignards and Silanes

(11)

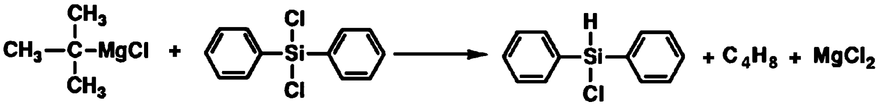
The activation energy for exchange appears to be lower than that for Grignard substitution. The exchange is more pronounced in tetrahydrofuran than in diethyl ether. Although frequently, the exchange is of no consequence, it can significantly alter final product distribution in some sterically constrained systems.

An elegant insertion-ring-expansion reaction, that involves halide exchange, ring-opening, and Grignard substitution, is the formation of silaoxacyclohexanes [22].



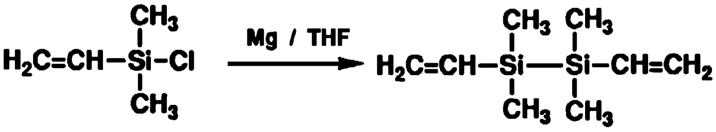
(12)

8. Sterically Hindered Grignards Can Reduce Silanes, Eliminating Olefin as a By-product


(13)

C. Process Chemistry with Ethers

There are three main batch process protocols for reaction of silanes with Grignard reagents. Addition of the silane to the Grignard reagent (normal addition) is preferred when full substitution is desired. The reaction is “single-pot”, in that the Grignard can be formed and then reacted without transfer. An example of a product produced by normal addition is triethylsilane. Addition of the Grignard to the silanes (reverse addition) is preferred when partial substitution of the silane is required. An example of a product produced by the reverse addition is diphenylmethylmethoxysilane. In situ formation of the Grignard in the presence of silane is preferred when the Grignard has poor solution stability or poor solubility. An example of a product produced by the in situ process is allyltrimethylsilane. Some hydridosilanes and vinylic silanes are reactive in the presence of magnesium metal and diethyl ether, eliminating the in situ method as an option. After a brief induction period, trichlorosilane reacts violently with magnesium in ether and tetrahydrofuran. Phenylhydridochlorosilanes [23] and vinylmethylchlorosilanes [24] undergo reactions similar to Wurtz coupling with magnesium in tetrahydrofuran. For example, divinyltetramethyldisilane forms from vinyldimethylchlorosilane.



$$H_2C{=}CH{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}Cl \xrightarrow{Mg\ /\ THF} H_2C{=}CH{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}\underset{CH_3}{\overset{CH_3}{Si}}{-}CH{=}CH_2 \qquad (14)$$

Commercially, continuous or continuous batch versions of these three protocols are generally employed [25].

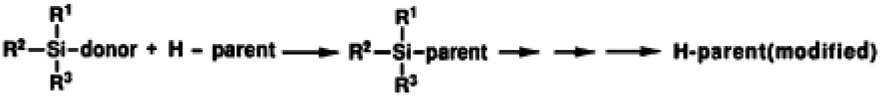
D. Process Chemistry Without Ethers

Chlorobenzene and bromobenzene can act both as reagents and solvents in the formation of multiply substituted phenylchlorosilanes such as triphenylchlorosilane [26,27]. The reactions run at elevated temperatures, 130–280°C, under atmospheric pressure.

Tetraethoxysilane and tetramethoxysilane can act as both solvents and reactants [28,29], or as cosolvents-catalysts in combination with benzene [30]. The use of tetraethoxysilane as a solvent-reactant has been important for a variety of continuous Grignard processes, since it allows an efficient recycle loop [31]. The continuous reactor portion of one such process disclosed in detail by Russian workers for diethyldiethoxysilane is depicted in Figure 1 [32] and may be contrasted with an earlier batch process [33]. Similarly, methylalkoxysilane and other alkylalkoxysilanes are reported as solvents-reactants in Grignard reactions, eliminating the need for ethereal solvents [34].

III. SILANE-BLOCKING AGENTS

Silane-blocking agents are employed to derivatize and protect various substrates during synthetic sequences. In a typical application, a silane-blocking group replaces an active hydrogen in a parent compound, a series of chemical transformations are performed on the modified parent compound, and finally, the blocking agent is removed.



$$R^2-\overset{R^1}{\underset{R^3}{Si}}-\text{donor} + H-\text{parent} \longrightarrow R^2-\overset{R^1}{\underset{R^3}{Si}}-\text{parent} \rightarrow \rightarrow \longrightarrow \text{H-parent(modified)} \tag{15}$$

The optimum blocking agent is one that derivatives the parent readily, withstands the transforming reactions, is readily deblocked, and has reasonable economics. Grignard substitution is one of the reactions frequently performed on silane-blocked intermediates. The most common blocking group, the trimethylsiloxy group, is not resistant to attack from Grignard reagents. For example, blocked phenoxybromides react with themselves, forming none of the desired Grignard reagent.

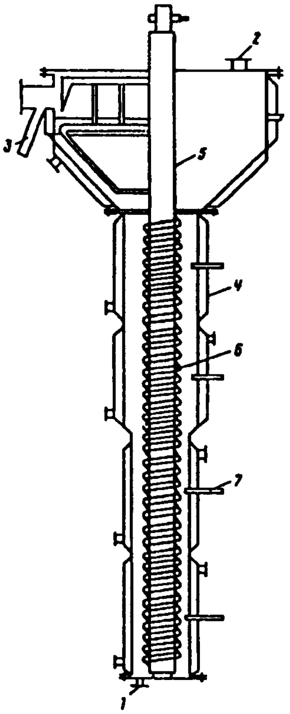
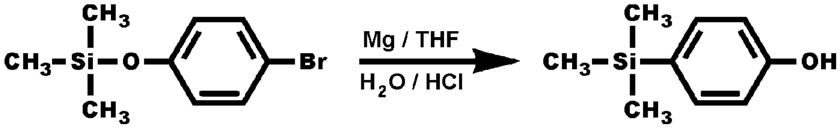


Figure 1. Continuous synthesis reactor for ethylalkoxysilanes: 1, input for reaction mixture; 2, input for magnesium; 3, output for product; 4, reactor body; 5, stirrer shaft; 6, spiral; 7, thermocouple well. (From Ref. 33.)



(16)

The choice of proper blocking agent for Grignard chemistry depends on economics, reaction conditions, and acceptable conditions for deblocking the final product. As illustrated in Table 1, all but the least sterically hindered silane-blocking agents have reasonable resistance to attack by Grignards and alkyl lithiums [35]. However, the reactions are reported for mild conditions. For example, the $t^{1/2}$ for the reaction of trimethylsiloxy-n-butanol with methylmagnesium bromide at room temperature is 48 hr. In contrast, the reaction of trimethylsiloxy-n-butanol with methylmagnesium chloride in refluxing tetrahydrofuran is virtually complete within 30 min.

IV. CONCLUSION

Although it is no longer crucial to the silicone industry, Grignard chemistry remains a vital and versatile method for the production of organosilanes. The technology of organosilanes derived from Grignards has been refined to control degree of substitution, utilize continuous processes, and eliminate ether solvents. The susceptibility of silane-blocking agents to attack by Grignard reagents has been defined, allowing both chemistries to be used in conjunction for the preparation of pharmaceuticals and specialty intermediates.

Table 1 Stability of Silylated Compounds to Synthetic Reagents[a]

		reagents			
Blocking group	Substrate	CH3MgBr in ether[a]	n-Butyl lithium[a]	Hydrochloric acid/THF[a]	Potassium fluoride/ methanol[a]
$(CH_3)_3Si$-	n-Butanol	48 hr	2 hr	<15 min	2 min
	Cyclohexanol	>48 hr	3 hr	<15 min	2 min
	t-Butanol	>48 hr	50 hr	<15 min	24 hr
$(C_2H_5)_3Si$-	n-Butanol	No reaction	24 hr	<15 min	2 hr
	Cyclohexanol	No reaction	>48 hr	<15 min	20 hr
	t-Butanol	No reaction	No reaction	<15 min	No reaction
t-BuMe$_2$Si	n-Butanol	No reaction	No reaction	>3 hr	No reaction
	Cyclohexanol	No reaction	No reaction	>3 hr	No reaction
	t-Butanol	No reaction	No reaction	No reaction	No reaction
Me$_2$CHCMe$_2$SiMe$_2$-	n-Butanol	No reaction	No reaction	16 hr	No reaction
	Cyclohexanol	No reaction	No reaction	30 hr	No reaction
	t-Butanol	No reaction	No reaction	No reaction	No reaction
t-BuPh$_2$Si-	n-Butanol	No reaction	No reaction	No reaction	100 hr
	Cyclohexanol	No reaction	No reaction	No reaction	No reaction
	t-Butanol	No reaction	No reaction	No reaction	No reaction

[a] *Source:* Ref. 36; times are +1/2 for Si-O-R bond scission.

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