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IODOTRIMETHYLSILANE—A VERSATILE SYNTHETIC REAGENT

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The last decade has witnessed an explosive growth in the use of organo-silicon reagents in organic synthesis.[1] Organosilicon reagents can be generally divided into three categories.

(i) Silylating agents for O and N silylation of alcohols, carboxylic acids, amines (e.g. chlorotrimethylsilane, hexamethyldisilazane) to provide volatile derivatives for glc. These silylations are also carried out for protection of the alcohol (–OH) group in organic synthesis.

(ii) Organosilanes for activation of an alkyl group towards reaction with electrophiles, for the synthesis of new carbon–carbon, carbon–oxygen, carbon–nitrogen and carbon–halogen bonds. This class of compounds includes allyltrimethylsilane, enol silyl ethers and a variety of other silylated intermediates.

(iii) Organosilanes, where the silicon atom is attached to a heteroatom (Me_3SiX) containing a moderately labile Si–X bond. Silicon forms strong bonds with oxygen and fluorine and relatively weak bonds with nitrogen, bromine, iodine, sulfur, and selenium[2] (Table 1). More prominent reagents belonging to this class of compounds include azidotrimethylsilane (Me_3SiN_3), cyanotrimethylsilane (Me_3SiCN), bromotrimethylsilane (Me_3SiBr) and iodotrimethylsilane (Me_3SiI). All these reagents have found extensive use in organic synthesis.[3,4]

Interested in the possible preparation of trivalent silicon cations, such as Me_3Si^+, we have explored some years ago a wide variety of its precursors under ionizing conditions. The weak Si–I bond offered a possible advantage in attempted ionization of iodotrimethylsilane Me_3SiI. Although these expectations were not realized, the studies aroused our interest in the remarkable reactivity of iodotrimethylsilane, as a hard–soft reagent.

Iodotrimethylsilane contains silicon as a hard acid and iodide as a soft base. This reagent therefore reacts very readily with organic compounds containing oxygen (a hard base) forming a strong silicon–oxygen bond. The iodide then acts as a strong nucleophile in a subsequent displacement step, thus

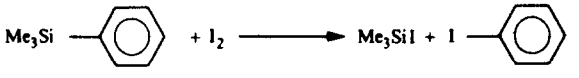
Table 1. Bond dissociation energies of organosilanes

Me_3SiX	D, KCal/mole[2]	Pauling's Bond Energies
Si-F	-	129.3
Si-O	-	88.2
Si-H	81±2	70.4
Si-C	76±2	69.3
Si-Si	67±2	42.2
Si-Cl	88±2	85.7
Si-Br	78.5±2	69.1
Si-I	69±2	50.9
Si-S	-	54.2

resulting in cleavage of carbon–oxygen bonds. This reactivity of iodotrimethylsilane has been exploited to carry out a large number of synthetically useful transformations. The rapid growth in the use of this versatile reagent warrants a review of its preparation and synthetic applications.

PREPARATION

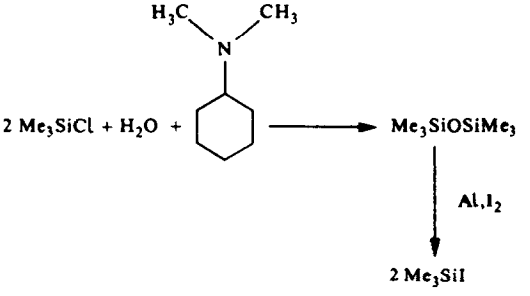
Whitmore *et al.*[5] developed the first convenient method of preparing iodotrimethylsilane by iodolysis of phenyltrimethylsilane. The reactants are heated under gentle reflux under anhydrous conditions and iodotrimethylsilane isolated by fractional distillation of the reaction mixture.



Another convenient method of synthesizing iodotrimethylsilane was developed by Voronkov *et al.*,[6] who obtained iodotrimethylsilane by the reaction of hexamethyldisiloxane with aluminum iodide.

$$Me_3SiOSiMe_3 + AlI_3 \longrightarrow 2Me_3SiI.$$

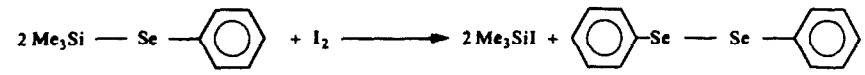
The product is obtained as a clear colorless liquid on fractional distillation of the reaction mixture under strictly anhydrous conditions. This method of preparation has recently been modified and iodotrimethylsilane can be obtained in >80% yield from chlorotrimethylsilane in a two step process.[7]



A less convenient method involves the halogen exchange between chlorotrimethylsilane and magnesium iodide.[8]

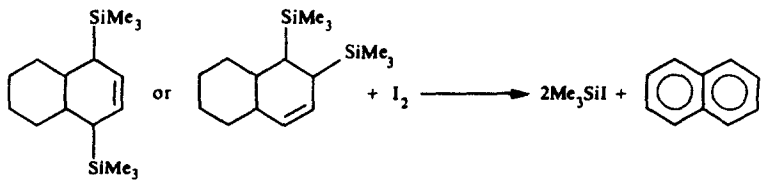
$$2\ Me_3SiCl + MgI_2 \longrightarrow 2\ Me_3SiI + MgCl_2.$$

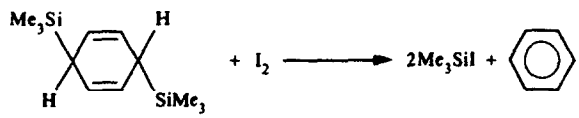
Detty *et al.*[9] have prepared iodotrimethylsilane from phenylselenotrimethylsilane and iodine.

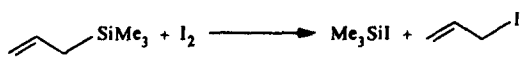


Iodotrimethylsilane can be isolated in very high yield by distillation from the reaction mixture. Diphenyldiselenide can be recycled to synthesize the precursor. This approach has also been used to prepare t-butyldimethylsilyl iodide.

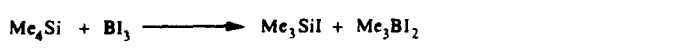
Some additional methods of synthesizing iodotrimethylsilane starting from less readily available materials are:

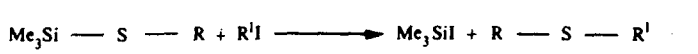


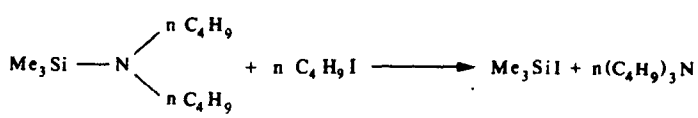


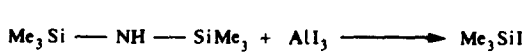


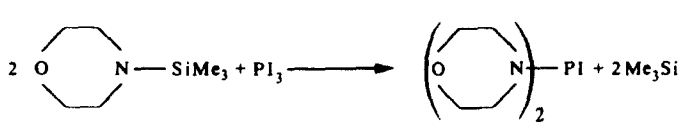
The following reactions have also been reported to yield iodotrimethylsilane as a product.











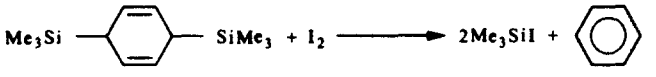
In situ *equivalents of iodotrimethylsilane.* The hydrolytic susceptibility of the Si–I bond in iodotrimethylsilane causes serious problems in several organic reactions involving acid sensitive compounds. In addition, iodotrimethylsilane should be prepared fresh and used immediately, because it fumes in air and turns purple on standing, making prolonged storage undesirable. Also, it is a relatively expensive commercial reagent, which has to be isolated by distillation from the reaction mixture. It is therefore highly desirable that synthetic methods for *in situ* generation of iodotrimethylsilane be developed.

We initially utilized the reaction of phenyltrimethylsilane with iodine at 110° for *in situ* generation of iodotrimethylsilane.[5,16]

This reagent system was found to be more efficient than iodotrimethylsilane for the cleavage of esters. Our observations were later confirmed by Benkeser *et al.*[17] However, there are two major drawbacks associated with the reagent.

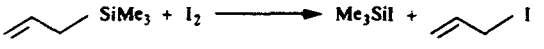
The high reaction temperature required for the iodolysis of phenyltrimethylsilane nullifies the inherent selectivity in some of the cleavage reactions of iodotrimethylsilane. An equivalent amount of iodobenzene is produced as a by-product which is very difficult to separate from some of the reaction products. Although we are able to circumvent this problem in certain special cases, no general method of separation of iodobenzene is available, except by very tedious column or gas chromatography. Therefore, we and others have developed alternative methods of *in situ* generation of iodotrimethylsilane or its equivalents.

Jung *et al.*[11] generated iodotrimethylsilane *in situ* from 3,6-bis-trimethylsilyl-1,4-cyclohexadiene and iodine, which is essentially an extension of the earlier method of Birkofer who obtained iodotrimethylsilane from the corresponding bis-trimethylsilyldihydronaphthalene derivatives.



However, this method involves the tedious synthesis of the starting diene.

Jung *et al.*[11] also prepared iodotrimethylsilane from the reaction of allyltrimethylsilane with iodine, forming 1-iodopropene as byproduct.



The formation of undesirable by products or tedious synthesis of precursors have led to use of the surprisingly simple and inexpensive alternative of chlorotrimethylsilane with sodium iodide in acetonitrile solution or with lithium iodide in chloroform and carbon tetrachloride.[18-22] When chlorotrimethylsilane is added to an acetonitrile solution of anhydrous sodium iodide, a yellow coloured solution (whose spectral characteristics are similar to those of a solution obtained from iodotrimethylsilane and acetonitrile in acetone-d_6) is obtained with immediate formation of white precipitate of sodium chloride.[19] A solution of equimolar proportions of acetonitrile and iodotrimethylsilane in d_6-acetone showed two absorptions at δ^1H (ext. tms) 2.24 and 0.27 due to methyl protons of acetonitrile and iodotrimethylsilane, respecitvely. Similarly, a solution of equimolar proportions of chlorotrimethylsilane, sodium iodide and acetonitrile also gave similar absorptions at δ^1H (ext. tms) 2.15 and 0.15. When these two solutions were mixed together, the mixture still showed only two absorptions at δ^1H 2.20 and 0.20 (tms as external standard), strongly suggesting the formation of similar type of complexes in both cases. Thus, we suggest the following mechanism.

$$MeCN + Me_3SiI \overset{\text{acetone}}{\rightleftharpoons} [Me\text{–}C{\equiv}\overset{+}{N}\text{–}SiMe_3]I^-$$

and

$$MeCN + Me_3SiCl + NaI \xrightarrow{\text{acetone}} [Ml\text{–}C{\equiv}\overset{+}{N}\,SiMl_3]I^- + NaCl$$

In addition, when iodotrimethylsilane is mixed with acetonitrile in the absence of acetone, a pale yellow precipitate is formed, which fumes in air, suggesting it could be due to the formation of the complex. Similar observations were made when chlorotrimethylsilane and sodium iodide were mixed together in acetonitrile. Further support in favor of the above mechanism is obtained from CMR measurements.

Thus, a solution obtained from iodotrimethylsilane and acetonitrile in acetone gave three absorptions at $\delta^{13}C$ (ext tms) 118.3, 2.2, and 2.8 due to nitrile carbon, methyl carbon of acetonitrile, and methyl carbon of silyl group, respectively. Similarly, a solution of sodium iodide, chlorotrimethylsilane, and acetonitrile in acetone gave three absorptions at $\delta^{13}C$ (ext tms) 118.5, 2.2, and 2.7, whereas, authentic samples of iodotrimethylsilane, chlorotrimethylsilane, and acetonitrile gave absorptions, respectively, at $\delta^{13}C$ (ext tms) 3.4, 4.1, and 118.5, and 2.0

The mixture of chlorotrimethylsilane/sodium iodide in acetonitrile was found to be a better reagent than iodotrimethylsilane in many of its reactions with organic substrates.

Schmidt *et al.*[18] are to be credited with the first use of this reagent system, when they showed it to be effective in their work on the reactions of carbonyl compounds.

Morita *et al.*[20,21] have also independently studied this reagent, although they did not consider that N-trimethylsilylacetonitrilium iodide formed in their reaction mixture. Machida *et al.*[22] have also described the use of chlorotrimethylsilane and lithium iodide in chloroform and carbon tetrachloride. Our NMR experiments support their contention that no iodotrimethylsilane is formed under their reaction conditions. With the chlorotrimethylsilane/sodium iodide reagent, one is however essentially confined to using acetonitrile as a solvent.

For the ideal *in situ* reagent, there are several factors to be considered. (a) The precursor should be available readily in high yeild. (b) *In situ* generation of iodotrimethylsilane should take place under mild conditions. (c) No by-products should be formed. Hexamethyldisilane fulfils all these criteria. Hexamethyldisilane is available in high yield via the Wurtz reaction of chlorotrimethylsilane. Hexamethyldisilane is known to react with iodine to give iodotrimethylsilane in quantitative yield.[23] The reaction can be carried out in a variety of solvents.

In conjunction with our work on chlorotrimethylsilane/sodium iodide/acetonitrile system,[24] we called attention to the use of hexamethyldisilane/iodine reagent as an *in situ* equivalent of iodotrimethylsilane.[25]

$$Me_3SiSiMe_3 + I_2 \xrightarrow{25\text{–}61^\circ} 2Me_3SiI.$$

We have developed this reagent further and shown that it is the best in situ *equivalent of iodotrimethylsilane.*

Seitz *et al.*[26] and Sakurai *et al.*[27] have independently demonstrated the utility of this reagent in organic synthesis.

PROPERTIES

Iodotrimethylsilane is a clear colourless liquid (b.p. 107°, 106–109°), which fumes in air. The product becomes discolored on storage, particularly when exposed to light and can be purified by distillation from copper powder. It has been well characterised by IR, Raman, ^1H NMR, ^{13}C NMR, ^{29}Si NMR, and by mass spectrometry.[28–31]

Due to its relative instability, iodotrimethylsilane should be preferentially prepared fresh or purified before using stored samples.

SYNTHETIC APPLICATIONS

Esters

Carboxylic acids are usually protected as esters in organic synthesis. Usually, esters are hydrolysed under basic or acidic conditions.[32] Reagents for non-saponifying hydrolysis (e.g. lithium iodide/alkylpyridines,[33] thiocyanate,[34] thiolate,[35] etc.) usually involve strong nucleophiles and high reaction temperatures. It is therefore necessary to develop mild neutral reagents for the conversion of esters to carboxylic acids.

Iodotrimethylsilane was found to be an extremely efficient reagent for the dealkylation of esters under strictly neutral conditions to yield the corresponding silyl esters which were hydrolysed upon aqueous workup to the carboxylic acids. Cleavage of esters was reported by us[36] and independently by others.[37] Carboxylic acids were obtained in very high yield on heating the esters with iodotrimethylsilane followed by quenching of the reaction mixture with water (Tables 2, 3).

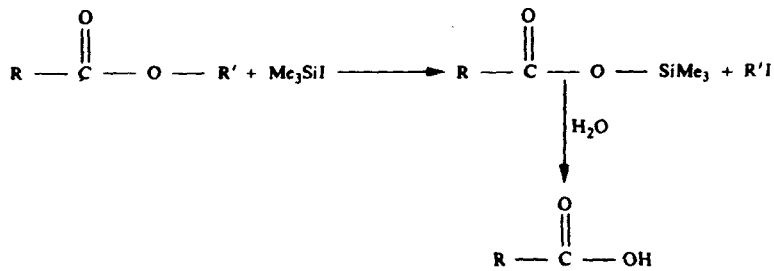
Table 2. Ester cleavage with (a) iodotrimethylsilane and (b) $PhSiMe_3/I_2$

Ester	Acid Yield [%] (a)	(b)
Methyl benzoate	80	95
o-bromobenzoate	81	98
phenylacetate	78	--
n-decanoate	75	90
cyclohexanecarboxylate	80	--
pivalate	55	--
Ethyl benzoate	72	--
phenylacetate	70	96
Benzyl Benzoate	86	92
Cyclohexanecarboxylate	90	--

Table 3. The dealkylation of esters by Me_3SiI $RCO_2R' + Me_3SiI \longrightarrow RCO_2SiMe_3 + R'I$

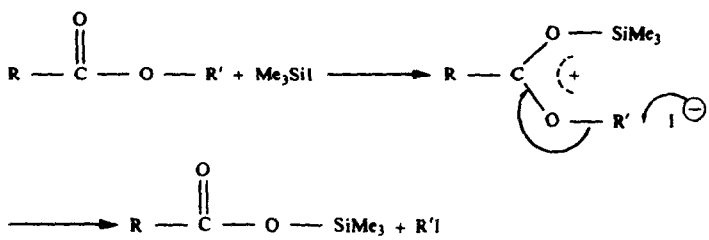
R	R'	Temp(C°)	Time(h)	Yield, %
CH_3	Me	50	8	--
Ph	Me	50	35	85
$CH_3(CH_2)_7$	Me	50	6	--
$CH_3(CH_2)_{12}$	Me	50	10	--
$PhCH{=}CH$	Me	50	4	--
$CH_3(CH_2)_7CH{=}CH(CH_2)_7$	Me	50	8	95
$CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7$	Me	50	20	85
1-Adamantyl	Me	50	20	90
$CH_3CO(CH_2)_4$	Me	50	5	84
2-Furanyl	Me	50	7	--
2-Thiophenyl	Me	50	24	80
$2\text{-}NH_2C_6H_4$	Me	80	1	82
CH_3	Et	50	24	--
Ph	Et	50	48	--
CH_3CH_2	Et	50	23	--
$(CH_3)_2CHCH_2$	Et	50	21	--
$CH_3(CH_2)_{14}$	Et	50	21	95
NH_2CH_2	Et	70	48	84
$AcNHCH_2$	Et	50	48	82
CH_3	i-Pr	50	10.5	--
CH_3	t-Bu	25	1/6	--
CH_3	CH_2Ph	25	0.5	--
Ph	i-Pr	50	23	--
Ph	t-Bu	25	0.5	90
Ph	CH_2Ph	25	1.5	--

The reaction proceeds via O-alkyl cleavage, and thus an equivalent amount of alkyl iodide is formed.

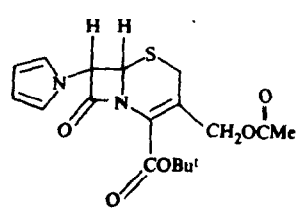


The reaction is general for all alkyl esters. Thus methyl and ethyl esters are cleaved cleanly in almost quantitative yield. Even hindered esters (e.g. methyl pivalate) are cleaved by this reagent. The present method allows selectivity between various esters, because benzyl and t-butyl esters react at a much faster rate than the methyl, ethyl and isopropyl esters. It is therefore possible to selectively cleave benzyl and t-butyl esters in the presence of methyl, ethyl, and isopropyl esters at 25°.

The reaction rates suggest the following mechanism for non-saponificative cleavage of esters by iodotrimethylsilane.



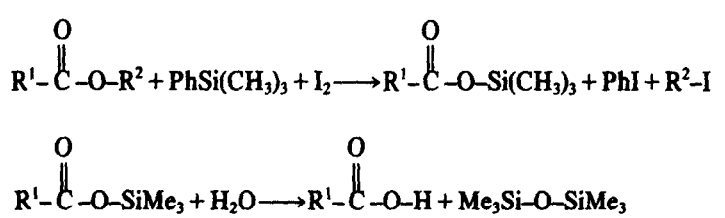
The selectivity of ester cleavage and the advantage of using neutral conditions is nicely illustrated in the attempted deprotection of the t-butyl ester group in the 7-pyrrolocephalosporin derivative.[38]



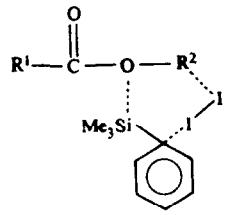
Because of the instability of pyrroles towards strong acids, the t-butyl group could not be removed by conventional acidic reagents.[39] Treatment with one equivalent of trifluoroacetic acid caused decomposition. However, reaction with iodotrimethylsilane followed by aqueous basic work up provided the free carboxylic acid in moderate yield. The selectivity of ester cleavage was demonstrated by the fact that the acetate was left under the reaction conditions.

From the mechanism of the reaction, it is quite clear that the aryl esters will not be cleaved by iodotrimethylsilane. This was found to be true thus allowing 100% selectivity of cleavage between aryl and alkyl esters.

Because of the difficulties associated with handling of iodotrimethylsilane, phenyltrimethylsilane/iodine reagent was also used for the cleavate of esters.[16,40] Phenyltrimethylsilane is known to react with iodine (see the section on *in situ* reagents) to yield iodotrimethylsilane and iodobenzene.



A concerted mechanism was suggested for the cleavage, rather than the *in situ* generation of iodotrimethylsilane and its subsequent reaction with the esters.

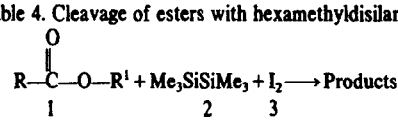


Subsequently, a great deal of attention has been focussed on the dealkylation of esters with *in situ* generated iodotrimethylsilane, such as chlorotrimethylsilane/sodium iodide reagent in acetonitrile. When chlorotrimethylsilane is added to an acetonitrile solution of sodium iodide, a yellow colored solution (whose spectral characteristics are similar to those of a solution obtained from iodotrimethylsilane and acetonitrile in acetone-d_6) is obtained with immediate precipitation of sodium chloride. Concurrently, other groups had also reported dealkylation of esters and other transformations with chlorotrimethylsilane/sodium iodide reagent.[18-21] The cleavage of esters is slightly slower with this reagent, than with iodotrimethylsilane.

Allyltrimethylsilane and 3,6-bis-trimethylsilyl-1,4-cyclohexa-2,5-diene have also been used as *in situ* precursors of iodotrimethylsilane[11] for the cleavage of esters.

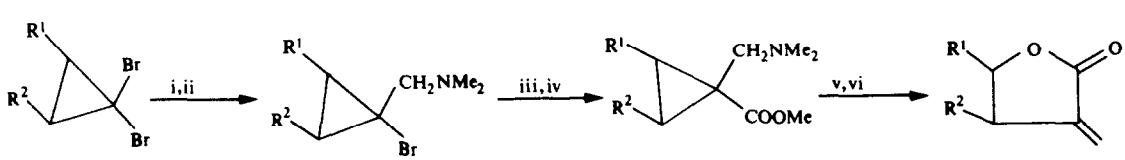
After the initial report on the use of *in situ* generated iodotrimethylsilane from hexamethyldisilane/iodine,[24] a detailed report was made of the utility of hexamethyldisilane/iodine reagent for dealkylation of esters[25] (Table 4). It was observed that the reaction with esters is catalysed by excess iodine in the reaction mixture. Other groups[26,27] have also utilized hexamethyldisilane/iodine reagent system for the cleavage of esters and other transformations.

Table 4. Cleavage of esters with hexamethyldisilane/I_2



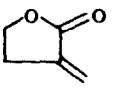
Substrate	1:2:3 (molar ratio)	Temp (°C)	Time(h)	Product(s)	Yield (%)
ethyl benzoate	1:0.66:0.66	61	48	benzoic acid	80
	1:0.6:0.7	25	48		98
benzyl benzoate	1:0.55:0.55	25	3	benzoic acid benzyl iodide	94 78
methyl,1-adamantane carboxylate	1:0.55:0.55 1:0.9:1.05	61 25	16 10	1-adamantane carboxylic acid	95 95
methyl cinnamate	1:0.55:0.55	61	16	cinnamic acid	92
ethyl phenylacetate	1:0.6:0.7 1:0.9:1.05	61 25	24 10	phenyl acetic acid	95 95

An elegant application of non-saponifying hydrolysis of esters has been demonstrated in the synthesis of α-methylene-γ-butyrolactones from the corresponding 1 - (N,N - dimethylaminomethyl)cyclopropanecarboxylate esters.[41] Because of the interesting physiological properties of several terpenes containing the α-methylene-γ-butyrolactone functionality, there have been many reports on the synthesis of this class of compounds.[42] Use of iodotrimethylsilane for this purpose is illustrated below.



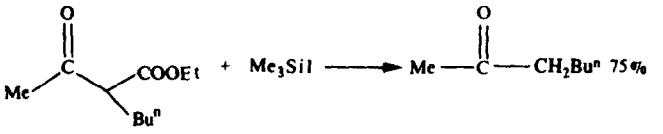
Reagents: (i) n-BuLi, −95°, THF (ii) $CH_2{=}\overset{+}{N}Me_2\ I^-$ (iii) n-BuLi or t-BuLi, −78°, THF (iv) $(MeO)_2C{=}O$ (v) Me_3SiI (vi) distill.

Thus, the starting dialkylaminocarboxylate ester undergoes dealkylation of the ester group followed by rearrangement in a highly stereo- and regioselective manner. The reaction takes place by treating the ester with iodotrimethylsilane, followed by distillative thermolysis of the resulting quaternary ammonium salt. This sequence of reactions was used for the synthesis of the highly unstable hemiterpene lactone, tulipalin.



This synthetic methodology is a significant improvement over corresponding methods utilising strongly acidic, aqueous conditions.[43]

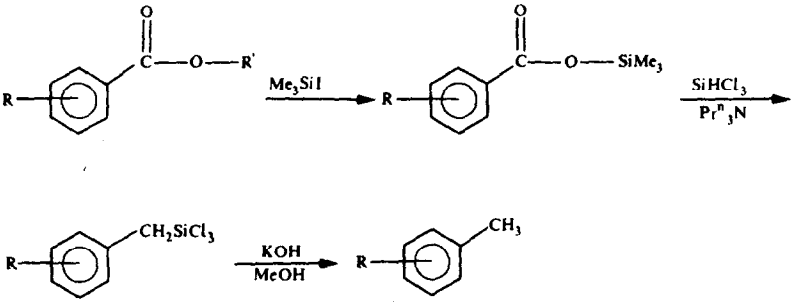
The dealkylation of esters has been used to synthesize trimethylsilylethyl oxalate by partial reaction of diethyloxalate with iodotrimethylsilane.[44] In another report, it was shown that β-keto esters and gem diesters undergo decarboalkoxylation on heating with iodotrimethylsilane.[45] Thus ketones and monocarboxylic acids are obtained on workup.



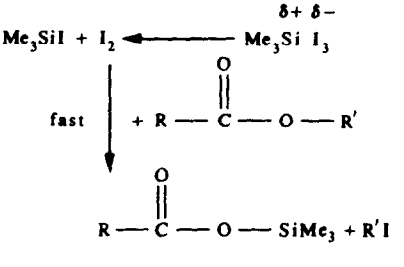
$Bu^nCH(COOMe)_2 + MeSiI \longrightarrow Bu^nCH_2COOH$ 68%

This procedure is a good alternative to the method of Krapcho involving heating of esters in wet DMSO in the presence or absence of alkali metal salts.[46]

The known formation of silylesters as intermediates has been exploited for the reduction of alkylbenzoates to the corresponding methylated aromatic compound in a three step sequence.[17]

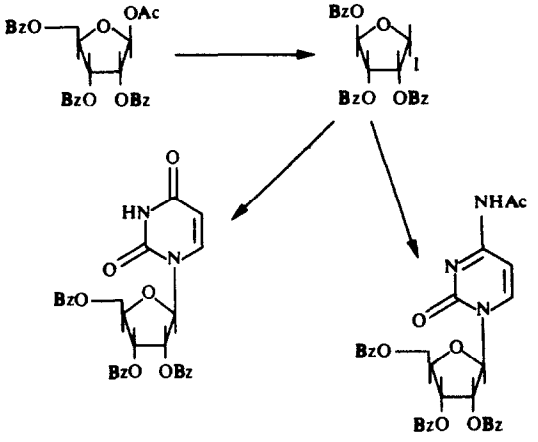


The catalytic effect of iodine on the reaction of esters with iodotrimethylsilane has been studied in detail. The following mechanism has been proposed.

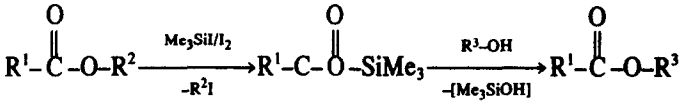


So far, we have only concentrated on that part of the molecule which retains the carboxylic group as the free acid. The fact that the other part of the molecule gives an alkyl iodide, has been exploited in carbohydrate chemistry for the synthesis of nucleosides.[47] Thus a glycosyl iodide was prepared by the reaction of a suitably blocked sugar derivative bearing an anomeric ester with iodotrimethylsilane. Reaction of the glycosyl iodide with some pyrimidine and purine nucleobases provided the correspond-

ing nucleosides. Thus, 1 - O - acetyl - 2,3,5 - tri - O - benzoyl - β - D - ribofuranose was reacted with iodotrimethylsilane and the resulting product coupled with silylated uracil to form 1 - (2,3,5 - tri - O - benzoyl - β - D - ribofuranosyl)uracil. Similarly, coupling with silylated cytosine, followed by acetylation yielded 1 - (2, 3, 5 - tri - O - benzoyl - β - D ribofuranosyl) - 4 acetamido - 2(1H) - pyrimidinone.

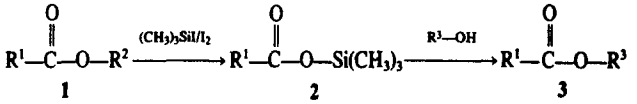


The formation of silylester intermediates in the dealkylation of esters has been exploited to develop iodotrimethylsilane mediated mild and neutral transesterification of esters,[48] the overall reaction being a composite of two successive transesterifications.



The transesterification procedure is general for aryl, alkyl and α,β-unsaturated carboxylic acid esters. Even hindered esters such as methyl pivalate underwent transesterification in good yield. However, the scope of the reaction is limited to primary and secondary aliphatic alcohols (Table 5).

Table 5. Transesterification of esters with iodotrimethylsilane



Substrate			Reaction Conditions	Yield [%]
R^1	R^2	R^3	1 ⟶ 2 °C, hr	
C_6H_5	CH_3	C_2H_5	60, 3	98
C_6H_5	CH_3	i-C_3H_7	60, 3	72
C_6H_5	C_2H_5	CH_3	25, 8	98
t-C_4H_9	t-C_4H_9	CH_3	80, 3	50
t-C_4H_9	CH_3	C_2H_5	80, 6	96
t-C_4H_9	CH_3	i-C_3H_7	80, 6	71
C_6H_5-CH=CH-	CH_3	C_2H_5	25, 6	98
C_6H_5-CH=CH-	CH_3	i-C_3H_7	25, 6	70
C_6H_5	CH_3	$C_6H_5CH_2$	60, 3	85
C_6H_5	CH_3	C_6H_5[b]	60, 3	40

Alkyl silyl ethers can be used in place of alcohols in the second step.

$$R'\text{–}\overset{O}{\overset{\|}{C}}\text{–O–SiMe}_3 + R^3\text{–O–SiMe}_3 \longrightarrow R'\text{–}\overset{O}{\overset{\|}{C}}\text{–O–}R^3 + Me_3SiOSiMe_3$$

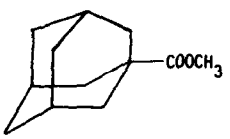
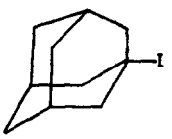
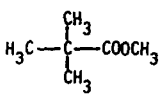
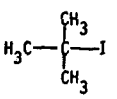
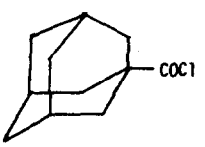
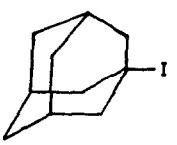
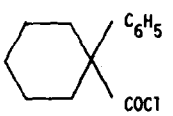
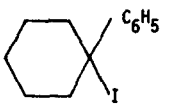
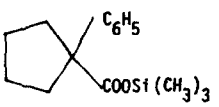
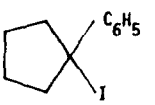
In their report on the dealkylation of esters, Jung *et al.*[37] described the formation of acyl iodides in high yield on prolonged exposure of esters to excess iodotrimethylsilane.

$$R\text{–}\overset{O}{\overset{\|}{C}}\text{–O–}R' + Me_3SiI \longrightarrow R\text{–}\overset{O}{\overset{\|}{C}}\text{–O–SiMe}_3 + Me_3SiI \longrightarrow R\text{–}\overset{O}{\overset{\|}{C}}\text{–I} + (Me_3Si)_2O$$

Ethyl palmitate was converted to palmitoyl iodide in 70% yield on reaction with 2.5 eq iodotrimethylsilane for 3 days at 75°.

During our studies on the reaction of methyl-1-adamantanecarboxylate with hexamethyldisilane/iodine reagent. it was observed that some 1-iodoadamantane is formed on prolonged heating of the reaction mixture.[49] By heating methyl-1-adamantanecarboxylate with 2 eq of hexamethyldisilane/iodine in the absence of solvent (~ 107°, b.p. of Me_3SiI), 1-iodoadamantane was obtained in 70% yield. The reaction is in fact general for tertiary alkyl carboxylate esters (Table 6).

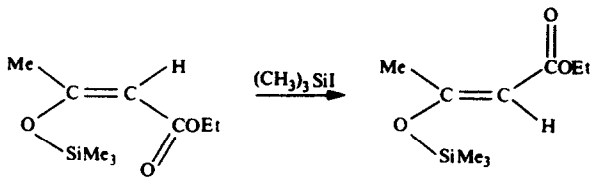
Table 6. Decarboxylative iodination of t-alkyl carboxylic acids

Substrate	Product	Yield [%][a]
		70
		90
		86
		86
		83

$$R\text{–}\overset{O}{\overset{\|}{C}}\text{–O–}R' \xrightarrow{-R'I} R\text{–}\overset{O}{\overset{\|}{C}}\text{–O–SiMe}_3 \longrightarrow R\text{–}\overset{O}{\overset{\|}{C}}\text{–I} \longrightarrow RI$$

Thus a general procedure has been developed for the halodecarboxylation of ester and acids (via the corresponding silyl esters and acyl chlorides).

Although esters in general are cleaved by iodotrimethylsilane, it was observed that *cis–trans* isomerization of certain crotonic acid esters can be catalyzed by iodotrimethylsilane at 100°.[50] Thus, a mixture of 86% *cis* and 14% *trans* β-trimethylsilyloxy crotonic acid esters was transformed on heating with catalytic amounts of iodotrimethylsilane at 100° for 2 hr into 98% *trans*, the thermodynamically more stable product.

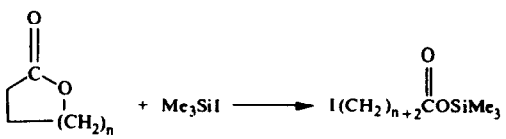


Similar results have been reported by other groups using halotrimethylsilanes.[51]

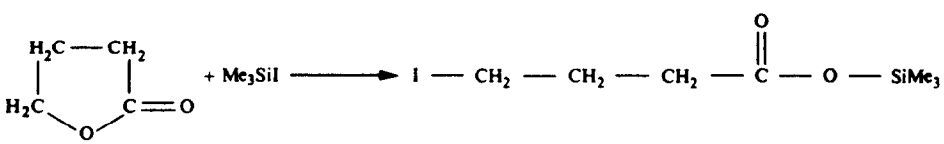
Lactones and carbonates

Because of the ready cleavage of esters with iodotrimethylsilane, it was quite obvious that lactones (especially with 4, 5 and 6 membered rings) would cleave at an appreciably faster rate.

Such cleavage of lactones provides an entry into ω-iodocarboxylic acids, which are highly versatile bifunctional synthons.

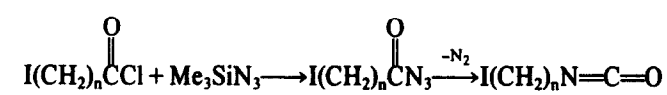


Voronkov *et al.*[52] initially reported the reaction of γ-butyrolactone with iodotrimethylsilane.

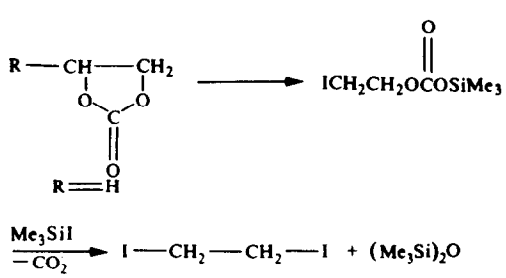


This reaction was developed further by Kricheldorf,[53] who treated a wide variety of lactones with iodotrimethylsilane and also with bromotrimethylsilane. Iodotrimethylsilane was found to be much more reactive than bromotrimethylsilane. These observations are consistent with our results on the cleavage of esters.

The iodoalkylesters and acids function as powerful alkylating agents. The iodo group could be converted to other functional groups like hydroxyl, mercapto, amino, etc. The bifunctional acids and acid chlorides are very important starting materials for a large number of industrially useful compounds. One of this class of compounds are the ω-haloalkyl isocyanates, obtained from the corresponding acyl chlorides, by reaction with azidotrimethylsilane followed by rearrangement of the product acyl azide.



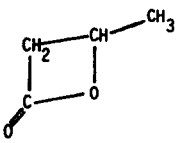
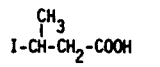
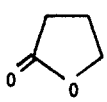
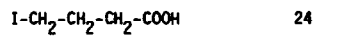
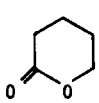
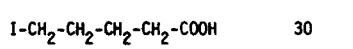
Cyclic carbonates were also found to react readily with iodotrimethylsilane, yielding 1,2-di-iodoalkanes.



Sultones could not be cleaved either with iodotrimethylsilane or bromotrimethylsilane, probably due to the low nucleophilicity of the sulfonyl oxygen, thereby preventing a strong interaction between silicon and the sulfonyl oxygen.

During the course of our research on chlorotrimethylsilane/sodium iodide reagent,[24] we have found that lactones could be cleaved readily with our reagent system (Table 7).

Table 7. Cleavage of lactones to ω-iodoacids with chlorotrimethylsilane/sodium iodide

Substrate	Product	Time (h)	Yield [%]
		10	81
		24	79
		30	84

β-, γ-, and δ-Lactones undergo ready cleavage on heating under reflux with chlorotrimethylsilane/sodium iodide in acetonitrile. β-Butyrolactone reacted somewhat faster than γ-butyrolactone due to the release of steric strain

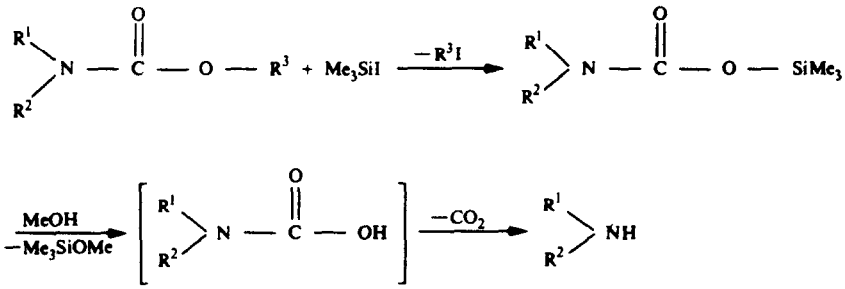
Carbamates and peptides

The carbamate functionality is a commonly used protecting group for primary and secondary amines. Whereas, many special groups have been developed for the protection of amines as carbamates so that the free amines can be recovered with ease, such carbamates are difficult to synthesise. Simple alkyl carbamates can be synthesized very easily, but require highly acidic reagents for deprotection to form the starting amines. The reagents commonly used for the cleavage of alkyl carbamates are strong base and strong acid. However, benzyl carbamates can be easily cleaved with acid[54] or hydrogenolysis[55] or photolysis.[56] t-Butyl carbamates can also be cleaved very readily with dilute acid.

In this context, based on the analogy with the reaction of esters, iodotrimethylsilane has proven to be a very general reagent to convert carbamates into the corresponding free amines, via the trimethylsilyl carbamates, as shown by Jung *et al.*[57] (Table 8).

Table 8. Reaction of alkyl carbamates with iodotrimethylsilane

R^1	R^2	R^3	Solvent	Temp/°C	Time/h	%Yield of(4)	%Yield of(5)
Ph	H	Me	$CDCl_3$	50	2·5	100	70
Ph	H	Et	$CDCl_3$	55	6	95(60)	--
Ph	Ph	Et	$CDCl_3$	50	8	--	93
H	H	CH_3Ph	$[CH_2]_4SO_2$	25	<0·1	100	--
$-CH_2CH_2OCH_2CH_2-$		Et	$CDCl_3$	60	3	100	--
C_6H_{13}	C_6H_{12}	Et	$CDCl_3$	60	2·5	100	92
$C_{10}H_{21}$	$C_{10}H_{21}$	Et	$CDCl_3$	60	2·5	100	89



The first step is a transesterification reaction, thus, the alkylcarbamate is converted to the trimethylsilyl carbamate. Treatment with methanol yields the free carbamic acid, which spontaneously loses CO_2 to provide the free amine. The reaction is equally valid for unsubstituted, mono and di-substituted carbamates. This method allows the deprotection of amines which are highly sensitive to other acidic or alkaline reaction conditions.

Because of the presence of a lone pair of electrons on the nitrogen, the carbonyl group is more polarised, thus facilitating the interaction of the carbonyl oxygen with silicon. For this reason, the carbamates react at a faster rate with iodotrimethylsilane, compared to the corresponding esters.

The chlorotrimethylsilane/sodium iodide/acetonitrile reagent system, was shown capable to convert alkyl carbamates into the corresponding amines in high yields[19] (Table 9).

Table 9. Decarboxylative cleavage of carbamates by chlorotrimethylsilane/sodium iodide reagent

$$R'R''NCOOR''' \xrightarrow{ClSiMe_3:NaI} R'R''NH + R'''I$$

(1) (2) (3) (4) (5)

Carbamates R	R'''	1 : 2 : 3 (molar ratio)	Reaction Conditions Time:Temp. (hr) (°C)	Products and Yields (4)	(5)		
H		1 : 2 : 3	1 / 25		76 100		
	CH_3	1 : 2 : 3	24 / 80	44			
	CH_3	1 : 2 : 3	24 / 80	46			
$-CH_2-CO_2H$		1 : 2 : 2	1 / 25	100	100		
$-CH_2-CO_2H$	$CH_3-C(CH_3)_2$	1 : 2 : 2	1 / 25	100	100		
$-CH_2-CO_2-CH_2-$ 	$CH_3-C(CH_3)_2$	1 : 2 : 2	1 / 25	$NH_2-CH_2-CO_2H$ 100	$CH_3-C(CH_3)_2-I$ 100		100

As is the case with esters, benzyl and t-butyl carbamates are cleaved faster than the methyl and ethyl derivatives. Benzyl carbamates are cleaved almost instantaneously at 25°, as are the t-butyl carbamates. On the other hand, methyl carbamates require heating under reflux for 24 h for complete cleavage to the corresponding amines. The reaction rate with the chlorotrimethylsilane/sodium iodide reagent is slower than with iodotrimethylsilane.

When benzyl-t-butyloxycarbonyl glycine was treated with chlorotrimethylsilane/sodium iodide, glycine was obtained with the deprotection of both ester and carbamate groups.

$$(CH_3)_3C\text{–}O\text{–}C(=O)\text{–}NHCH_2C(=O)\text{–}O\text{–}CH_2\text{–}C_6H_5 \xrightarrow{Me_3SiCl/NaI} (CH_3)_3CI + CO_2 + C_6H_5CH_2I + H_2N\text{–}CH_2\text{–}C(=O)\text{–}OH$$

Seitz *et al.*[26] using the hexamethyldisilane/iodine reagent have also shown that t-butoxycarbonyl group can be removed under mild conditions from N(t-butoxycarbonyl)-L-valine in 83% yield with no racemisation of the product. Our results[25] with the hexamethyldisilane/iodine reagent indicate that the reagent is very selective compared with chlorotrimethylsilane/sodium iodide. For example, carbamates can be cleaved cleanly in the presence of a benzyl ester.

$$\text{Boc–Gly–OBzl} \xrightarrow[5\text{ min}]{Me_3SiSiMe_3/I_2} \text{Gly–OBzl} \xrightarrow[15\text{ min}]{Me_3SiSiMe_3/I_2} \text{Gly}$$

Iodotrimethylsilane is a very attractive reagent for peptide synthesis, because esters and carbamates are the most common blocking groups used in peptide synthesis. The acid catalysed deblocking of peptides results in the formation of t-butyl and benzyl carbocations, which often leads to t-butylation and benzylation of the aromatic residue in the peptide chain. This alkylation reaction does not occur on deblocking of peptides with iodotrimethylsilane, because the alkyl residue is cleaved via the S_N2 mechanism, thereby circumventing the formation of the highly reactive carbocations.

Stammer *et al.*[58] have examined in detail the reaction of several N-benzyloxy and N-t-butoxycarbonyl peptides with iodotrimethylsilane, by following the reaction by ^1H NMR. The reagent was found to be very selective (Table 10).

Table 10. Deprotection of peptides with iodotrimethylsilane.

Peptide	Solvent	Equiv. TMSI	Temp/°C	Time for removal/h Z/Boc	Benzyl/NO_2
Boc-Val-Tyr(Bzl)·OMe	CD_3CN	1·2	25	0·1	--
Boc-Val-Tyr(Bzl)·OMe	CD_3CN	3·6	50	0·1	2
Z-Pro-Phe·OH	$CDCl_3$	2·4	25	0·1	--
Boc-Pro-Phe·OMe	$CDCl_3$	1·2	25	0·1	--
Z-Pro-ΔPhe·OMe	$CDCl_3$	1·2	25	0·1	--
Boc-Leu-ΔLeu·OMe	$CDCl_3$	1 2	25	0·1	--
Z-Cys(Bzl)·OH	DMF	3·6	50	0·1	--
Z-Arg(NO_2)·OH	CD_3CN	3·6	50	0·1	--
Boc-His(Bzl)·OH	$CDCl_3$	3·6	50	0·1	--

O-Benzyltyrosine was cleaved without the formation of any rearrangement products. None of the side chain protecting groups were affected by treatment with iodotrimethylsilane. This method will probably find wide use in solid phase peptide synthesis as well.

Phosphine oxides and phosphoramides

It was suggested[59,60] that in the presence of atoms containing non-bonding electrons, silicon–iodine bond may be ionised to yield complex cations containing silicon (IV). Phosphine oxides and phosphoramides belong to this class of compounds. Beattie *et al.*[61] were able to isolate a crystalline adduct between trimethylphosphine oxide and iodotrimethylsilane. The structure was formulated as $Me_3\overset{+}{P}\text{–}O\text{–}SiMe_3I^-$.

The adduct was characterised by IR spectroscopy and conductivity measurements. Other groups have later on prepared some more tris[alkyl or aryl] trimethylsilyloxyphosphonium iodides by the reaction of the corresponding phosphine oxides with iodotrimethylsilane (Table 11).[62,63]

Similar ionic adducts have been isolated by the reaction of iodotrimethylsilane and bromotrimethylsilane with tris(dimethylamino) phosphine oxide.[63]

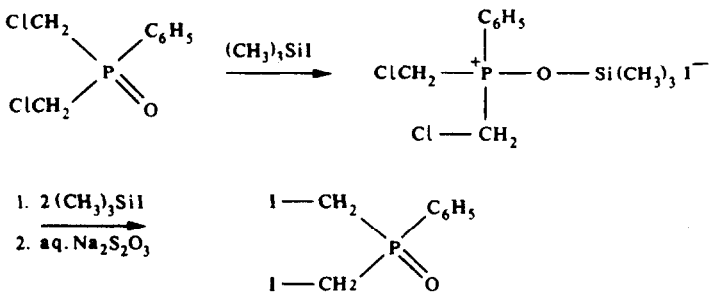
$$(Me_2N)_3P{=}O + Me_3SiX \longrightarrow [(Me_2N)_3POSiMe_3]^+X^-.$$

Table 11. Synthesis of iodo (trimethylsilyloxy) phosphoranes from phosphine oxides[61-63]

Phosphine Oxide	Product	Yield [%]
$(CH_3)_3$ P=O	$(CH_3)_3\overset{+}{P}OSiMe_3I^-$	--
$(CH_3CH_2)_3$ P=O	$(CH_3CH_2)_3\overset{+}{P}OSiMe_3I^-$	88
$(Me_3SiOCH_2)_3$ P=O	$(Me_3SiOCH_2)_3\overset{+}{P}OSiMe_3\overset{-}{I}$	98
$(Ph)_3$ P=O	$(Ph)_3\overset{+}{P}OSiMe_3I^-$	80
(CH_3) (CH_3CH_2) (Ph) P=O	$(CH_3)(CH_3CH_2)(Ph)\overset{+}{P}OSiMe_3\overset{-}{I}$	--
$[(CH_3)_2N]_3$ P=O	$[(CH_3)_2N]_3\overset{+}{P}OSiMe_3I^-$	--

Conductomeric studies showed that the equilibrium for formation of these adducts in dichloromethane lies well to the right. These results were also confirmed by ^{31}P NMR studies. The known kinetic characteristics of reaction involving HMPT-catalysed racemisations or substitutions of silicon halides can be interpreted in terms of such phosphonium intermediates.[64-66]

Because of the potential of these trimethylsiloxy phosphonium salts in organic synthesis, these studies have been extended to alkylphosphine oxides bearing substituents on the alkyl group, with some very interesting results.[67] When bis[chloromethyl]phenyltrimethylsilyloxyphosphonium iodide was treated with iodotrimethylsilane, halide exchange was observed.



In addition to chlorine, bromine and tosylate groups can also undergo displacement with iodotrimethylsilane.

$$(X{-}CH_2)_3P{=}O \xrightarrow{(CH_3)_3SiI} (I{-}CH_2)_3P{=}O$$
$$X = Cl,\ Br,\ O\text{-}Tos$$

These studies have been extended to chlorophosphines and chlorophosphoranes (Table 12, Table 13).

$$R_{3-n}PCl_n + nMe_3SiI \longrightarrow R_{3-n}PI_n + nMe_3SiCl$$
$$R_{5-n}PCl_n + nMe_3SiI \longrightarrow R_{5-n}PI_n + nMe_3SiCl$$

This method allows the preparation of iodophosphines and iodophosphoranes under mild neutral conditions, in a very high yields, compared to the usual metal iodide exchange method[68] which provides relatively lower yields and a tedious work up, considering the sensitivity of the products towards moisture and oxygen.

This method allows the easy preparation of diphenylphosphinous iodide and ethanephosphonous di-iodide, which could not otherwise be prepared using metal iodides, but were prepared by cleavage of dimeric and tetrametic starting materials containing phosphorous-phosphorous bond.[69] Some of these iodophosphines and iodophosphoranes are finding increasing utility as reagents in organic synthesis.[70,71]

Table 12. Synthesis of iodophosphines

Product	Reaction conditions temp. [°C], time, solvent	Yield [%]
PJ_3	20°, 0.5 h, benzene	92
$(C_2H_5)_2NPJ_2$	-50°, 0.5 h, hexane	94
$[(C_2H_5)_2N]_2PJ$	-20°, 0.5 h, ether	90
$C_2H_5PJ_2$	20°, 1.0 h, benzene	74
$t\text{-}C_4H_9PJ_2$	-20°, 0.5 h, ether	97
$(C_2H_5)_2PJ$	20°, 1.0 h, benzene	80
$(C_6H_5)_2PJ$	20°, 1.0 h, benzene	77

Table 13. Synthesis of iodophosphoranes

Substrate	Reaction conditions temp. [C°], time, solvent	Product	Yield [%]
PCl_5	20°, 1.0 h, benzene	PJ_5	98
$C_6H_5PCl_4$	20°, 1.0 h, benzene	$C_6H_5PJ_4$	91
$(C_6H_5)_3PBr_2$	0°, 1.5 h, dichloromethane	$(C_6H_5)_3PJ_2$	86
$(C_6H_5)_4PBr$	20°, 1.0 h, acetonitrile	$(C_6H_5)_4PJ$[d]	80

Phosphonate and phosphate esters

Phosphonate and phosphate esters are of particular importance in synthesis, because of their utilisation as intermediates in the synthesis of oligonucleotides and for the synthesis of phosphonate analogoues of biological phosphate esters. One of the crucial steps in the synthesis of these compounds is the dealkylation of the esters to yield the free acids.

Although aryl phosphonates can be cleaved with hydroxide[72] and benzylic esters can be cleaved by hydrogenolysis,[73] there is no general method available for the dealkylation of the simple alkyl esters. It should be noted that 2-cyanoethyl esters[74] and 2,2,2-trichloroethyl esters[75] can yield free acids by treatment with ammonium hydroxide and Zn-dust respectively, they consistute rather special cases. Simple alkyl esters are usually cleaved under harsh conditions by treatment with conc. hydrochloric acid at high temperatures.[76] It is imperative therefore to find mild and neutral reagents for the cleave of phosphate and phsophonate esters, in order to prepare the free acids containing other acid sensitive functional groups or to prepare phosphonic acid derivatives of nucleosides, lipids and carbohydrates.

The use of halotrialkylsilanes for the cleavage of phosphonates was initially investigated by Voronkov[77] and Schwarz[78] and later on by Rabinowitz.[79] They found that some phosphonate and phosphate esters undergo transesterification to the corresponding trialkylsilyl esters on treatment with chlorotrialkylsilanes. It was also observed that the silyl esters could be converted to the free phosphonic acids on quenching with water, thus providing an entry to phosphonic acids and phosphoric acids under mild, neutral conditions.

However,the chlorosilanes require high temperatures and very long reaction times for the transesterification. It was discovered by Voronkov[77] Rudinskas[80] and McKenna[81] that bromotrimethyl(ethyl)silane offered a dramatic reduction in the time and temperature of the transesterification. Therefore, it was anticipated that iodotrimethylsilane and its *it situ* equivalents would be better reagents than bromotrimethylsilane. This expectation has been borne out by the simultaneous publications of Morita,[20] Machida,[22] Mastalerz[82] and Blackburn.[83] Whereas Morita and Machida used chlorotrimethylsilane with sodium iodide and lithium iodide respectively, Mastalerz[82] and Blackburn[83] achieved the same results with iodotrimethylsilane (Tables 14–17).

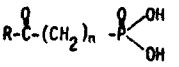
Table 14. Reaction of dialkyl phosphonates with chlorotrimethylsilane/sodium iodide

Substrate R	R'	NaI (Equiv.)	Temp. (°C)	Time (min)	Yield (%)
$PhCH_2$	Me	1.0	r.t.	15	100
Cl_3C	Me	1.0	r.t.	15	100
$(MeO)_2CH$	Me	1.0	r.t.	15	100
EtOCH=CH	Me	1.0	r.t.	15	100
MeCO	Et	1.0	20-40	30	>98
$MeOCOCH_2$	Et	1.0	20-40	30	>98
Et_2NCO	Et	1.0	20-40	30	>98
H_2NCOCH_2	Et	1.0	20-40	30	>98
$NCCH_2$	Et	1.0	20-40	30	>98
$NCCH_2$	Et	1.1	r.t.	15	100

Table 15. Dealkylation of $RPO_3R'_2$ by Me_3SiCl–LiI

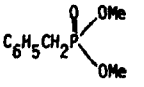
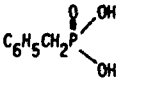
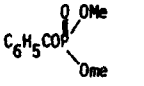
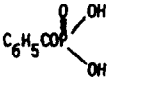
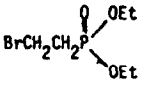
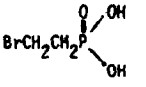
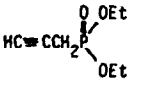
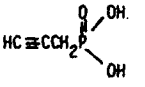
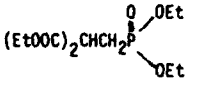
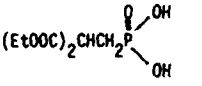
Substrate R	R'	Yield[a]
$EtOCOCH_2$	Et	100%
$MeOCOCH_2$	Et	100%
$EtOCOCH_2$	$PhCH_2$	100%
$EtOCO(CH_2)_3$	Et	100%
$EtOCO(CH_2)_3$	$PhCH_2$	100%
$CH_3(CH_2)_4COCH_2$	Me	100%
$EtSCH_2$	Et	100%
CH_2=CH	Et	>95%
CH_3CH=CH cis	n-Bu	>95%
$PhCH_2$	Et	100%

Table 16. Preparation of oxoalkanephosphonic acids from esters

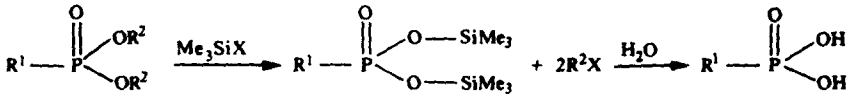


R	n	Yield [%]
CH_3	0	76
C_2H_5	0	78
$n\text{-}C_3H_7$	0	76
CH_3	1	84
$i\text{-}C_3H_7$	1	82
$t\text{-}C_4H_9$	1	79

Table 17. Dealkylation of phosphonate esters with iodotrimethylsilane

Substrate	Product
	
	
	
	
	

A comparison of the data in Tables 14–17 shows that all three reagent systems are equally effective for the dealkylation of dialkylphosphonates. The resulting bis(trimethylsilyl)phosphonates were converted into free phosphonic acids by treatment with water or methanol. The phosphonic acids were isolated as salts by reaction with aniline or p-anisidine. The reaction can be depicted in general as:

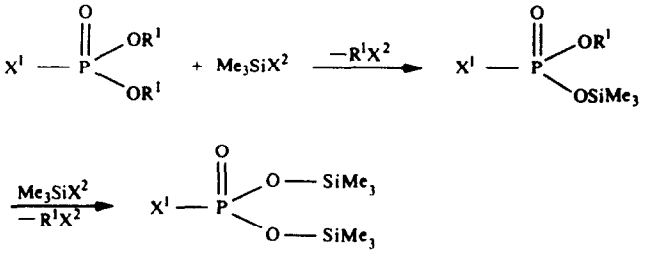


An examination of the data shows that dialkylphosphonates are selectively cleaved in the presence of other functional groups like carboxylate esters, carbon–carbon multiple bonds, and haloalkyl groups (although some halogen exchange has been reported). It is especially valuable for dealkylation of acylphosphonate and aroylphosphonate esters. Dealkylation of 2-oxoalkanephosphonate esters has been studied in detail by Mastalerz *et al.*[82]

The dealkyaltion reaction is general for alkyl esters, but aryl esters cannot be cleaved as expected from earlier observations with carboxylate esters.[36,37] The selectivity for hydrolysis of alkyl versus aryl

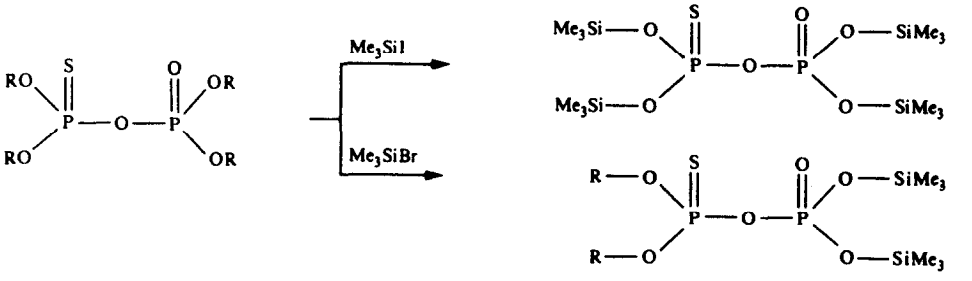
phosphate esters is complementary to the variety of methods available for the selective cleavage of aryl esters. On the other hand, iodotrimethylsilane cannot be used for achieving selectivity between various alkyl groups in mixed phosphonate esters. McKenna[84] has shown that such selectivity is possible with bromotrimethylsilane. Recently, Yoshii *et al.*[85] have demonstrated the stepwise and selective dealkylation of phosphotriesters with phenylthiotrimethylsilane.

Michalski *et al.*[86] have studied the transesterification of compounds of the general formula $X^1P(O)(OR')_2$, where X^1 denoted a reactive ligand attached to phosphorus. These compounds may be of biochemical interest. They found that O,O-dialkylphosphorochloridates, bromidates, thiolates and O,O-dialkylphosphoramidates react with iodotrimethylsilane to yield the corresponding trimethylsilyl esters without altering the P–Cl, P–Br, P–S and P–N bonds. The reaction was shown to proceed in a stepwise manner, thus allowing the preparation of mixed silyl alkyl esters.



X^1 = Cl, Br, NR_2, NHR, NH_2, SR, H

The reaction could also be used for esters of polyphosphoric acid, with preservation of the P–O–P bond.

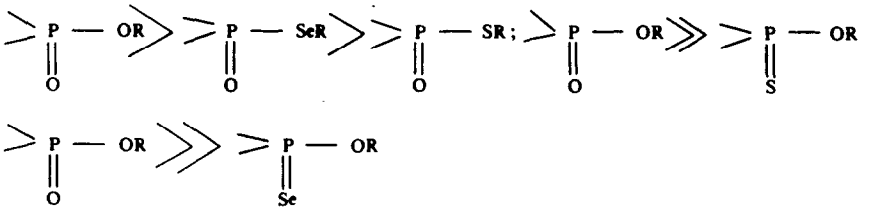


These reactions show that the nature of the product can be altered by changing from the less reactive bromotrimethylsilane to the more reactive iodotrimethylsilane. This indicates the lower reactivity of the thionophosphoryl moiety relative to the phosphate, towards halotrimethylsilane reagents.

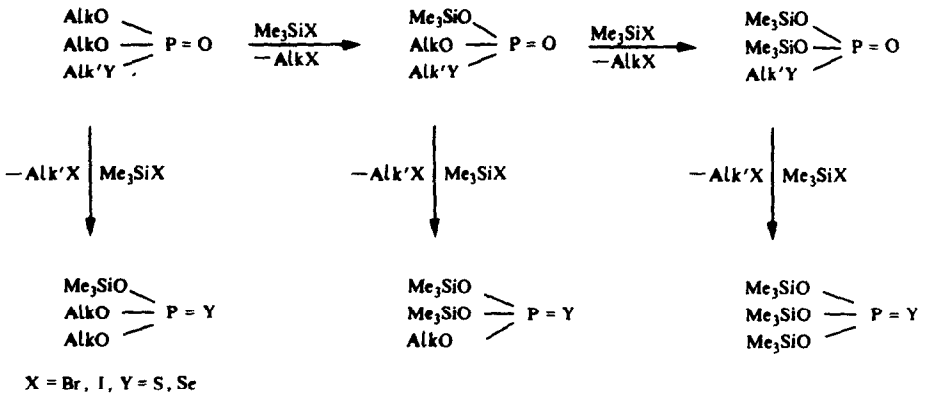
The synthetic and mechanistic aspects of the reaction of iodotrimethylsilane with thio and seleno analogs of phosphate and phosphonate esters have been examined in detail by Michalski *et al.*[87] They have studied the reaction of iodotrimethylsilane with various esters of phosphorothioic and phosphoroselenoic acids of general structures $(RO)_2(RY)P=O$ and $(RO_3)P=Y$, where Y = S, Se and R = alkyl.

The reactions resulted in the replacement of alkyl groups by trimethylsilyl groups, as expected from our previous knowledge about the behaviour of phosphonate esters. No S-trimethylsilyl and Se-trimethylsilyl substituted esters were detected among the reaction products. Thus the transesterification of O–R, S–R and Se–R esters always leads to the corresponding O–$SiMe_3$ ester containing the thiophosphoryl and selenophosphoryl groups.

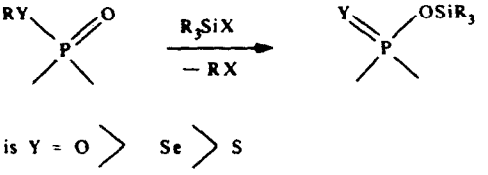
From the large number of different esters studied, the following order of reactivity towards iodotrimethylsilane was established.



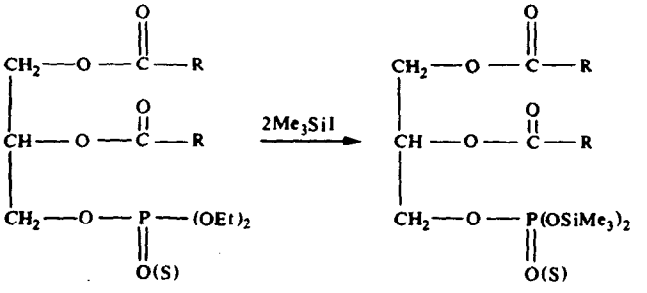
The two types of transesterification reactions observed with iodotrimethylsilane are depicted below.

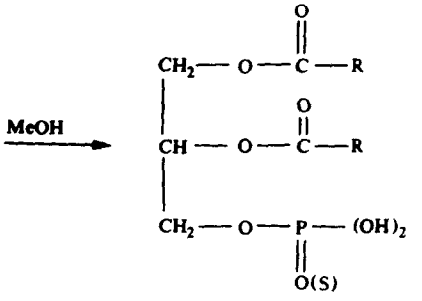


Again, as expected, iodotrimethylsilane was shown to be much more reactive than bromotrimethylsilane. The general order of reactivity for the reaction:



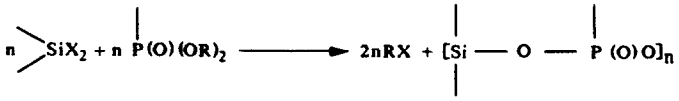
The transesterification of phosphoryl and thiophosphoryl compounds has been applied to the synthesis of phosphatidic acids.[88]



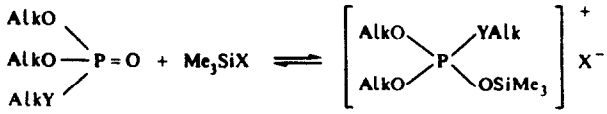


This reaction highlights the selectivity between carboxylic ester and phosphate ester cleavage. This methodology significantly simplifies the synthesis of phosphatidic acids, providing new possibilities in the chemistry of phospholipids.

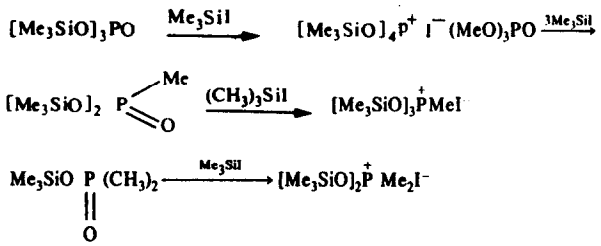
Finally, these transesterifications have potential for the synthesis of silicon and phosphorous containing polymers.[89]



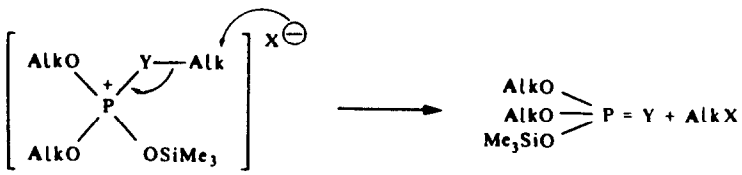
Regarding the mechanism of dealkylation of phosphonate and phosphate esters, the reaction involves as the first step, the nucleophilic attack by the phosphoryl oxygen on silicon, resulting in the formation of the phosphonium salt intermediate. This is analogous to the previously discussed reaction of phosphine oxides and phosphoramides with iodotrimethylsilane.



Such adducts have been isolated from tris(trimethylsilyl)phosphate and also from the silyl esters of methylphosphonic and dimethylphosphonic acid.[90]

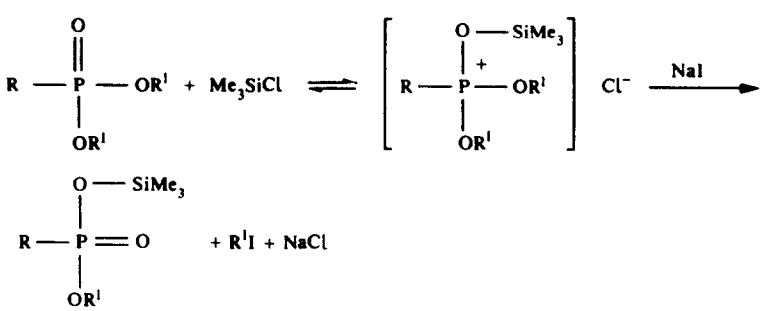


The second step involves the attack of halide on one of the alkyl groups to yield the alkyl halide and the corresponding trimethylsilyl ester.

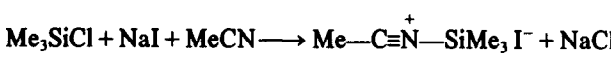


Thus, the total reaction involves initially the reversible formation of a phosphonium salt intermediate in a fast step, followed by slow dealkylation. It was shown by ^{31}P NMR studies that in the reaction of iodotrimethylsilane with an ester bearing a P=O phsophoryl group, the equilibrium for the formation of the phosphonium salt lies well over towards the intermediate, thus enabling its direct observation. These mechanism proposals were also confirmed by conductance studies on the reaction system and also by investigation of the stereochemical course of the corresponding reaction of an optically active model thiophosphonate, where complete racemisation was observed.

The mechanism of cleavage of phosphonate esters using chlorotrimethylsilane/sodium iodide/acetonitrile has been suggested not to involve the intervention of iodotrimethylsilane.



However, it has been shown that chlorotrimethylsilane reacts instantaneously with NaI in acetonitrile to yield N-trimethylsilylacetonitrilium iodide.

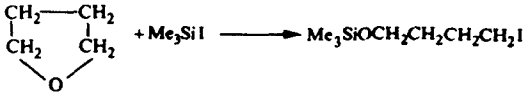


Therefore, it is quite likely that the acetonitrilium salt is the active reagent in these reactions. NMR studies do not indicate the formation of iodotrimethylsilane from chlorotrimethylsilane and lithium iodide in carbon tetrachloride or chloroform in significant amounts.[91] Therefore, the direct reaction of chlorotrimethylsilane is favoured in this case.

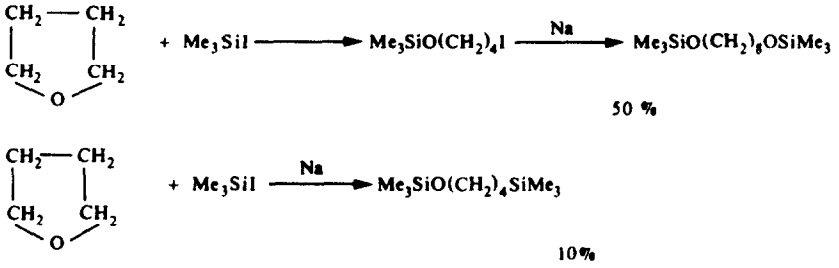
Ethers

The first indication of the reaction of iodotrimethylsilane with ethers can be attributed to Kruerke *et al.*,[8] who observed the cleavage of diethyl ether being used as a solvent during the attempted preparation of iodotrimethylsilane by halide exchange of chlorotrimethylsilane with magnesium iodide.

These investigators also studied the reaction of tetrahydrofuran with iodotrimethylsilane, but did not characterise the product. Voronkov *et al.*[92] examined the reaction of tetrahydrofuran in detail. At 60°, trimethyl-(-4-iodobutoxy)silane was obtained in quantitative yield.



They also observed that in the presence of sodium, the nature of products was entirely different



This reaction provides a convenient synthesis of 1,8-octanediol. The reaction has also been studied with Li, K, and Mg.[93] It was also observed that the unstable trimethyl-(4-iodobutoxy)silane reacts with iodotrimethylsilane to yield 1,4-di-iodobutane in 85% yield.

$$Me_3SiI + Me_3SiO(CH_2)_4I \longrightarrow I(CH_2)_4I + Me_3SiOSiMe_3$$

The analogous reaction with tetrahydropyran was conducted at a slightly higher temperature (90°), with the formation of a mixture of (5-iodopentyloxy)trimethylsilane and 1,5-di-iodopentane.[94]

Although the dealkylation reaction of chloro and bromosilanes with alkyl and alkyl aryl ethers has been known for a long time, the cleavage of alkyl aryl ethers with iodotrimethylsilane was only recently examined by three independent groups, i.e Olah *et al.*[16] Jung *et al.*[96] and Voronkov *et al.*[96] (Table 18).

Table 18. Cleavage of methyl aryl ethers with iodotrimethylsilane

Ar	Reaction Time (h)	Yield [%]
C_6H_5-	21	99
p$CH_3C_6H_4$-	18	99
pFC_6H_4-	35	98
pClC_6H_4-	40	98.5
pBrC_6H_4-	36	98
C_6F_5-	52	98

$$Ar—O—R + (CH_3)_3SiI \longrightarrow Ar—O—Si(CH_3)_3 + RI \xrightarrow{H_2O} ArOH$$

The intermediate aryloxytrimethylsilanes can be isolated if desired or hydrolysed directly to the corresponding phenols. Methyl ethers were found to be more reactive than other alkyl aryl ethers. Ortho-substitution also lowered the yield of the desired dealkylated product. This method is a substantial improvement over the available methods which require harsher reaction conditions and are in general limited to methyl aryl ethers.

Dealkylation of alkyl aryl ethers with phenyltrimethylsilane/iodine reagent was found to be more efficient than with the performed reagent (Table 19). These observations were reconfirmed by Benkeser *et al.*[17]

Table 19. Cleavage of alkyl aryl ethers with $PhSiMe_3$–I_2

Ether	Reaction time h	Phenol, Yield %
Anisole	4	90
Phenetole	4	84
Phenyl n-propyl ether	6	50
Benzyl phenyl ether	4	80
Methyl 2-naphthyl ether	4	86

Many alkyl ethers are used as protecting groups for alcohols in organic synthesis. The most commonly used groups are benzyl, trityl, THP(tetrahydropyranyl), and t-butyl. These groups are removed by hydrogenolysis or by treatment with acids. A variety of highly specific protecting groups are also available. Although methyl ethers have been used extensively as protecting groups for phenols, they have not been used in aliphatic systems because of the difficulty of their removal. Aliphatic ethers including methyl ethers can be removed with boron trihalides, other Lewis acids, and *in situ* generated HI. However, most of these methods provide mixtures of products. It is in this context that Jung *et al.*[95] have studied in detail the simple and efficient dealkylation of aliphatic ethers with iodotrimethylsilane, providing the deprotected alcohols and phenols in high yield (Table 20).

$$R—O—R^1 + Me_3SiI \longrightarrow R—O—SiMe_3 + R^1—O—SiMe_3 + R^1I + RI.$$

Although the reaction is totally regiospecific for alkylaryl ethers (only phenols are formed), cleavage of dialkyl ethers provided mixture of products depending upon the nature of R and R^1 and the reaction conditions. In the cleavage of cyclohexyl methyl ether, higher selectivity was observed by lowering the reaction temperature. Trityl, benzyl, and t-butyl ethers react at a much faster rate than other alkyl ethers, thus permitting their selective cleavage. Dialkyl ethers react much faster than alkyl aryl ethers, allowing the cleavage of dialkyl ethers in the presence of alkyl arylethers. Alkyl methyl ethers react faster than methyl esters, so that the ethers can be cleaved cleanly in the presence of the methyl esters. The reactions are cleaner in the presence of propene as an acid scavenger.

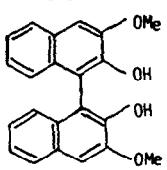
When the dialkyl ethers were treated with excess iodotrimethylsilane, the corresponding alkyl iodides were obtained in high yield thus providing a convenient synthesis of alkyl iodides directly from the corresponding ethers.

$$R—O—R^1 + Me_3SiI \longrightarrow R—O—SiMe_3 + R^1OSiMe_3 + R^1I + RI$$
$$\downarrow \text{ excess } Me_3SiI$$
$$R^1I + RI + Me_3SiOSiMe_3$$

Table 20. Dealkylation of ethers by iodotrimethylsilane

$$ROR' + Me_3SiI \longrightarrow ROSiMe_3 + R'OSiMe_3 + R'I + RI$$

1 2 3 4 5 6

Ethers			Products and Yields			
R	R'	Time (h)	3	4	5	6
C_6H_{11}	Me	6	95	5	95	5
C_6H_{11}	Me	2	90	10	90	10
C_6H_{11}	Et	12	48.7	22.5	77.5	51.3
C_6H_{11}	Et	16	0	0	100	100
C_6H_{11}	i-Pr	48	0	0	100	100
C_6H_{11}	t-Bu	<0.1	100	0	100	0
C_6H_{11}	CH_2Ph	<0.1	100	0	100	0
C_6H_{11}	CPh_3	<0.1	100	0	100	0
$CH_3(CH_2)_5CHCH_3$	Me	8.5	86	0	100	7
3β-cholestanyl	Me	12	100	0	100	0
4-oxocyclohexyl	Me	2.5	100	0	100	0
CH_2CH_2 (glyme)	2Me	9	67	33	100	0
$HC{\equiv}CC(Me)_2^-$ $C{\equiv}CCH_2$	Me	1.3	0	0	100	100
$PrCOCHEtCH_2$	t-Bu	<0.1	100	0	100	0
$i\text{-}PrCOC(Me)_2CH_2$	t-Bu	<0.1	100	0	100	0
$Ph_3CCH_2CO(CH_2)_5$ $(CH_2)_5$	CPH_3	<0.1	100	0	100	0
C_2H_5	Et	70	0	0	100	100
$-CH_2(CH_2)_2CH_2-$		<0.1	100	0	100	0
$-CH_2(CH_2)_2CH_2-$		75	0	0	100	100
C_6H_5	Me	48	100	0	100	0
C_6H_5	Me	21	100	0	100	0
$p\text{-}C_6H_4$	2Me	30	100	0	100	0
$o\text{-}BrC_6H_4$	Me	125	100	0	100	0
$m\text{-}BrC_6H_4$	Me	120	30	0	30	0
$p\text{-}BrC_6H_4$	Me	120	100	0	100	0
$o\text{-}NH_2C_6H_4$	Me	12	100	0	100	0
$m\text{-}NH_2C_6H_4$	Me	22	100	0	100	0
$p\text{-}NH_2C_6H_4$	Me	22	100	0	100	0
$m\text{-}CH_3C_6H_4$	Et	140	100	0	100	0
		26	100	0	100	0

Ethers can also be cleaved with chlorotrimethylsilane/sodium iodide in acetonitrile as shown by Olah *et al.*[19] and Morita *et al.*[20] (Tables 21 and 22). The reaction of ethers with chlorotrimethylsilane/sodium iodide proceeds faster than with iodotrimethylsilane itself. Detty[14] has demonstrated the usefulness of phenylselenotrimethylsilane/iodine reagent for dealkylation of ethers. Hexamethyldisilane/iodine[25–27] (Tables 23 and 24) and allyltrimethylsilane/iodine[10] can also be used for efficient cleavage of ethers.

Table 21. Dealkylation of ethers by chlorotrimethylsilane/sodium iodide reagent.

$$ROR' \xrightarrow{ClSiMe_3:NaI} ROH \rightarrow RI$$
(1) (2) (3) (4) (5)

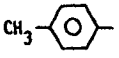
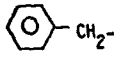
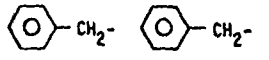
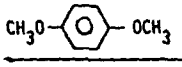
Ethers R	R'	1: 2: 3	Reaction Conditions Time/Temp. (h) (°C)	Products and Yields (4)	(5)
	CH_3-	1: 2: 2	48/82	100	
	CH_3-	1: 2: 2	9/82	95	
	C_2H_5-	1: 2: 2	40/82	90	
	CH_3-	1: 2: 2	16/82	0	93
		1: 2: 2	16/82	0	88
	Me	1: 2: 2	16/82	35	43
		1: 2: 2	5/25	90	10
		1: 4: 4	48/82	98	

Table 22. Dealkylation of ethers with chlorotrimethylsilane/sodium iodide reagent

Substrate	Temperature (°C)	Time(h)	Yield [%]
C_6H_5-O-CH_3	70-75	27	81
p-$CH_3C_6H_4$-O-CH_3	70-75	28	83
C_6H_5-O-CH_2-C_6H_5	50	1·5	90

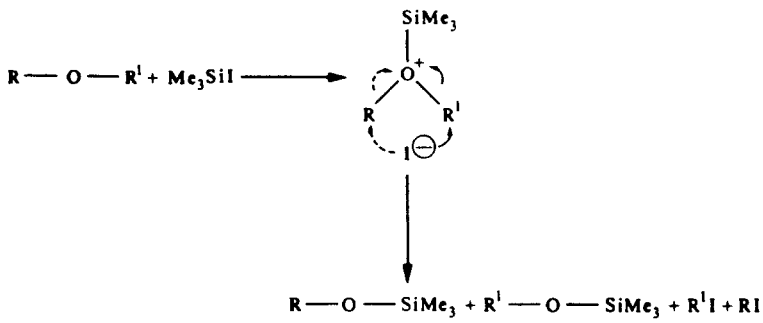
Table 23. Dealkylation of ethers with hexamethyldisilane/I_2

Substrate	1:2:3 (molar ratio)	Temp(°C)	Time	Product(s)	Yield (%)
anisole	1:0.66:0.66	61	48 h	phenol	95
phenetole	1:0.66:0.66	61	124 h	phenol	30
	1:1:2	61	16 h	phenol	98
benzyl methyl ether	1:1:2	61	2 h	benzyl iodide	87
cyclohexyl methyl ether	1:0.66:0.66	25	16 h	cyclohexanol	95
	1:1:2	~100	4 h	cyclohexyl iodide	98
cyclohexyl ethyl ether	1:1:2	61	3 h	cyclohexyl iodide	98

Table 24. Dealkylation of ethers with hexamethyldisilane/I_2

Substrate	Product	Yield [%]
C_6H_5-O-CH_3	C_6H_5-O-Si$(CH_3)_3$	75
C_6H_5-O-CH_2-CH=CH_2	C_6H_5-O-Si$(CH_3)_3$	82
C_6H_5-O-CH_2-C_6H_5	C_6H_5-O-Si$(CH_3)_3$	100(nmr yield)

The cleavage of ethers with iodotrimethylsilane and its *in situ* analogs occurs via an ionic mechanisms. There is the interaction of the electron deficient silicon with the lone pairs on oxygen resulting in the formation of a trimethylsilyl oxonium ion followed by nucleophilic displacement on carbon by iodide.

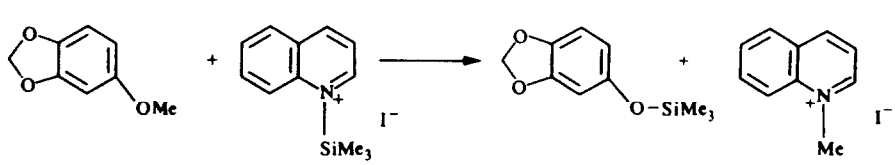


These results are consistent with the observed catalysis by iodide ion.[19]

Dealkylation of ethers with iodotrimethylsilane has already found many interesting applications, iodotrimethylsilane has been successfully used for the demethylation of 1,4-dimethoxyphenanthrene by Weber *et al.*[97]

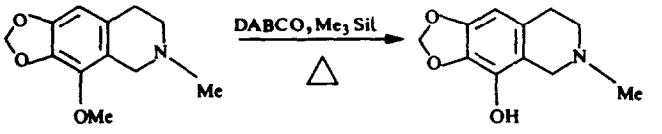
1,4-Phenanthraquinone was isolated due to the *in situ* oxidation of the hydroquinone intermediate. It is interesting to note that conventional demethylating agents like LiI/collidine and sodium ethanethiolate in DMF failed to provide any demethylated product.

Although there are methods available for the selective cleavage of methylenedioxy group in polyoxygenated alkaloids,[98] no general method was available for the selective demethylation of a methyl ether in the presence of a methylenedioxy group. Such a transformation was achieved with iodotrimethylsilane, but only when the usual solvents were replaced by quinoline.[99]

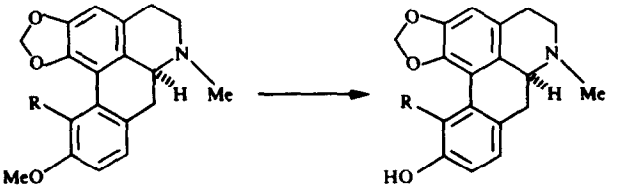


Thus, sesamol methyl ether was demethylated with the concomitant formation of N-methylquinolinium iodide. The methyl iodide formed in the reaction reacts with quinoline to form the quaternary ammonium salt. 2,3-Methylenedioxyphenol was obtained in a similar manner from the corresponding methyl ether.

The active reagent for these dealkylations is most probably the N-trimethylsilylquinolinium iodide. When this reaction system was tried for demethylation of alkaloid hydrocotarnoline, a complex mixture of products was obtained due to side reaction with simultaneously produced methyl iodide. However, replacement of quinoline by the stronger base, i.e. 1,4-diazabicyclo-octane (DABCO), resulted in a clean reaction.[100]

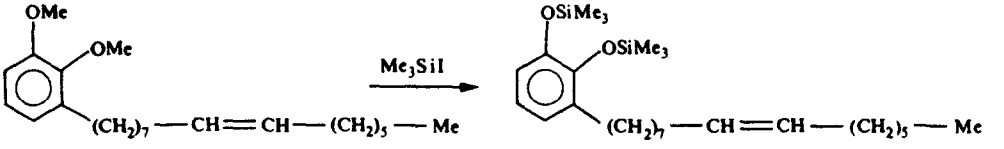


Similarly, S-(+)-mecambroline was obtained from S-(+)-laurelin in 54% yield.



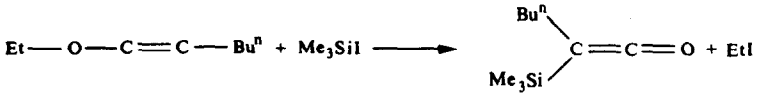
This methodology is very useful in the conversion of abundantly available polyoxygenated alkaloids into less oxygenated congeners for chemical correlation and for biological evaluation.

The demethylation of aryl methyl ethers with iodotrimethylsilane in the absence of any base has been applied to the synthesis of urushiol derivatives,[101] which are the vesicant principles of poison ivy and related plants.



Eisenbraun *et al.*[102] have compared iodotrimethylsilane and boron tribromide for the demethylation of certain catechol ethers. They found that in this application, Me_3SiI is less reactive than BBr_3. Iodotrimethylsilane was found to be more effective than boron tribromide for the cleavage of less accessible methoxy groups.

A novel application of dealkylation of ethers with iodotrimethylsilane is the synthesis of hitherto relatively inaccessible trimethylsilyl ketenes from the corresponding 1-alkoxy-1-alkynes.[27]

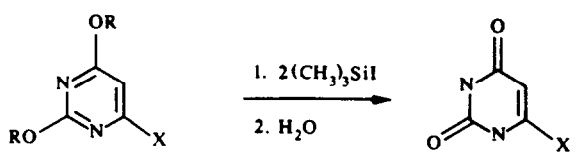


Bis(trimethylsilyl)ketene was prepared in a similar manner.

6-Substituted uracils are usually prepared by acid hydrolysis of 2,4 - dialkoxy - 6 - substituted pyrimidines, but under acidic conditions, the products usually undergo extensive decomposition. Iodotrimethylsilane has been found to be an excellent dealkylating agent for 2,4-dialkoxypyrimidines[103] (Table 25).

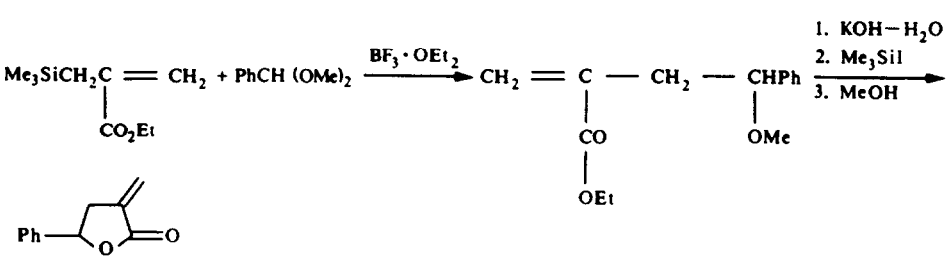
Table 25. Hydrolysis of 2,4-dialkoxypyrimides by iodotrimethylsilane

R	X	Reaction time	%yield
CH_3	SO_3H	<15 min	quantitative
CH_3	SO_2NH_2	<15 min	94
CH_3	Cl	10 h	quantitative
CH_3	CH_3	<15 min	87
CH_3	F	6 h	67
C_2H_5	H	1 h	35
		2 h	53
		14 h	quantitative
$C_6H_5CH_2$	Cl	15 min	quantitative



This method was particularly useful for the preparation of uracil-6-sulfonic acid (X=SO_3H) which undergoes loss of bisulfite under the usual acidic hydrolysis conditions.

One of the most useful applications of iodotrimethylsilane in organic synthesis has been the synthesis of α-methylene-γ-butyrolactones, the key structures in a number of naturally occuring sesquiterpenes with potential cytotoxic activity.[104] Sakurai *et al.*[105] have shown that α-methylene-γbutyrolactones can be obtained in very high yield in a two step synthesis from 2 - alkoxycarbonylallyltrimethylsilanes and acetals.

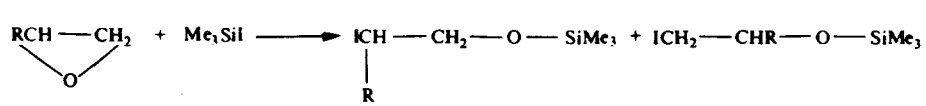


The crucial step involves demethylation of the methyl ether with iodotrimethylsilane followed by ring closure to the lactone.

Epoxides

In analogy with the reaction of iodotrimethylsilane with ethers, it is not unexpected that epoxides will also cleave with the possibility of formation of different products depending upon the reaction conditions.

Voronkov *et al.*[106] reported the cleavage of ethylene oxide and propylene oxide to yield the corresponding iodoalkylsilyethers.

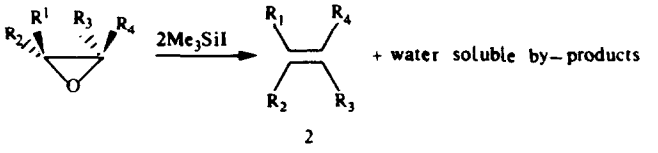


R = H, CH_3

When the reaction was performed in the presence of sodium metal, the corresponding olefins were obtained.

$$Me_3SiOCH_2CHIR + 2Na \longrightarrow CH_2{=}CHR + Me_3SiONa + NaI$$

Krief *et al.*[107] have developed a simple method for the deoxygenation of epoxides by treatment with 2 molar equivalents of iodotrimethylsilane.

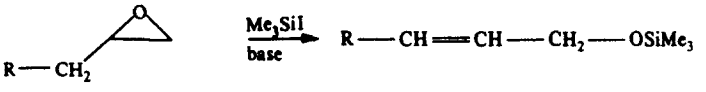


2

$R_1{=}R_3{=}CH_3(CH_2)_7$, $R_2{=}R_4{=}H$ Yield 89%
$R_1{=}R_4{=}H$, $R_2{=}R_3{=}CH_3(CH_2)_7$ Yield 83%

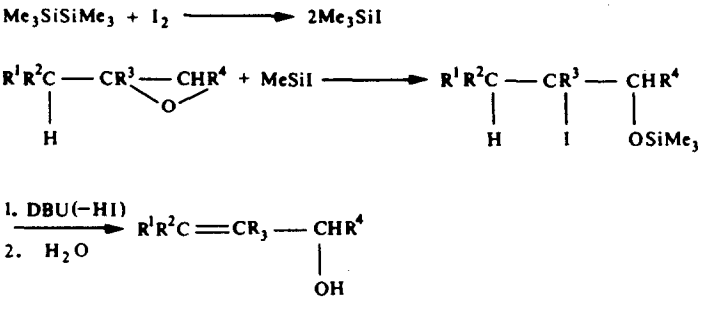
The reaction was found to be 100% regiospecific. The reaction has been proposed to go through the intermediate 9 - iodo - 10 - trimethylsilyloxyoctadecane. The reactions are stereospecific (>97%) with the product olefins possessing the same stereochemistry as the starting epoxide. Iodotrimethylsilane thus provides an efficient method for the transformation of epoxides to olefins, an important step in the synthesis of all *trans* squalene, for the structure determination of natural products and for the stereospecific isomerisation of olefins.

In an attempt to prepare allylic alcohols, Detty[108] studied the reaction of iodotrimethylsilane with epoxides, but found that the reaction was not clean.



Mixtures of deoxygenated and ring opened products were obtained. The analogous reactions with trimethylsilyl trifluoromethanesulfonate[109] or with t-butyldimethyliodosilane[108] (prepared from the reaction of iodine with phenylseleno - t - butyldimethylsilane) yield the desired allyl trimethylsilyl ethers in high yield.

Sakurai *et al.*[110] have solved this problem by carrying out the reaction with iodotrimethylsilane (generated *in situ* from hexamethyldisilane and iodine) in a stepwise manner.



The whole conversion is carried out in a one pot operation (Table 26). The essential reagent for the process is hexamethyldisilane which is thermally and hygroscopically stable, non-toxic and readily available. The reactivity of iodotrimethylsilane towards epoxides was found to be higher than that of trimethylsilyl trifluoromethanesulfonate.

Kraus *et al.*[111] have also demonstrated the efficient preparation of allylic alcohols from the reaction of epoxides with iodotrimethylsilane followed by dehydrohalogenation with DBN. The reaction conditions were found to be compatible with esters and cyclic acetals (Table 27). The mild conditions and simplicity of operation offer distinct advantages over other methods. the iodotrimethylsilane mediated procedure is

Table 26. Conversion of epoxides to allylic alcohols with hexamethyldisilane/I_2 and DBU

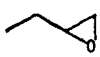
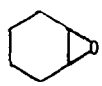
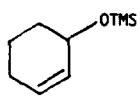
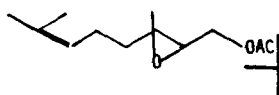
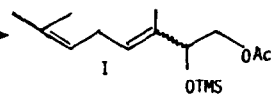
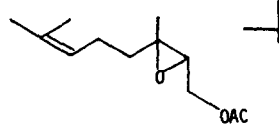
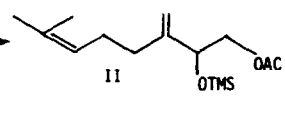
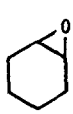
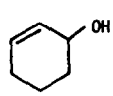
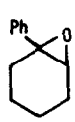
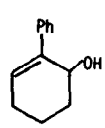
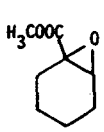
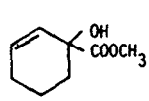
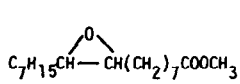
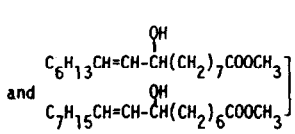
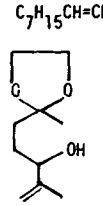
Epoxide	Product	Yield [%]
		70
		81
		53 I/II(85/15)
		63 I/II(35/65)

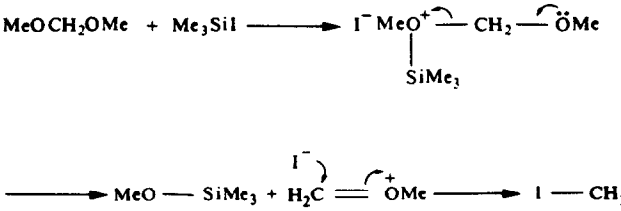
Table 27. Preparation of allylic alcohols from epoxides with iodotrimethylsilane

Epoxide	Allylic Alcohol	Yield [%]
		79
		68
		21
		75
		50

complementry to the organoselenium method of Sharpless[112] in that trisubstituted epoxides afford secondary allylic alcohols.

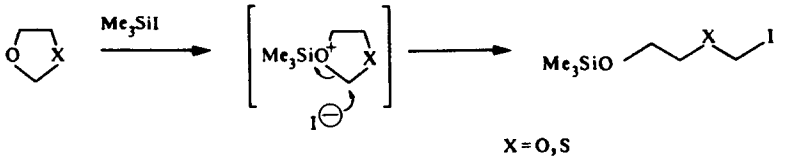
Acetals

In analogy with the reaction of ethers, the reaction of acetals with iodotrimethylsilane is expected to give α-iodoethers. These expectations have been fully realised in the reaction of dimethoxymethane(methylal).[113] Iodomethylmethyl ether was obtained in high yield.

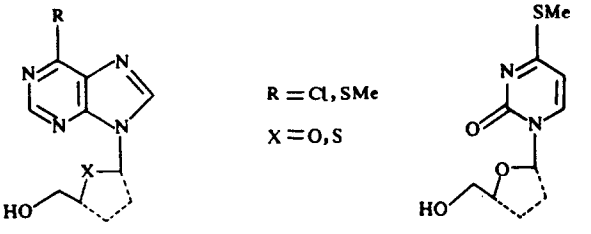


Iodomethyl methyl ether is a useful reagent for the synthesis of methoxymethyl ethers from alcohols[114] and for iodomethylation of aromatic substrates.[115] Iodomethyl methyl ether is preferable to chloromethyl methyl ether which is always contaminated with bis(chloromethyl)ether and is highly carcinogenic. Iodomethyl methyl ether shows enhanced reactivity compared to chloromethyl methyl ether.

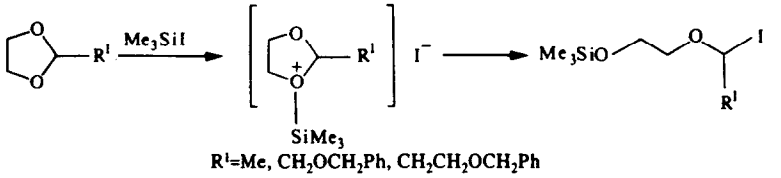
The reaction has been extended to 1,3-dioxolanes and 1,3-oxathiolanes to prepare the corresponding α-iodoethers as alkylating agents.[116]



Thus both iodomethyltrimethylsilyloxyethyl ether (X=O) and the corresponding sulfide (X=S) react with several purine and pyrimidine anions to provide nucleoside analogs of some potent antiviral compounds.



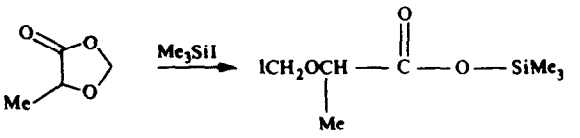
The analogous cleavage of 2-substituted 1,3-dioxolanes provides the synthesis of acyclic sugar analogues which are lacking only C(3′) or the C(3′)–C(4′) bond.[117]



It is interesting to note that the benzyloxy group is not cleaved under the reaction conditions. These alkylating agents were used to prepare several adenine and purine derivatives.

This methodology can be used to synthesise a variety of potential antibiotic, antitumor, and antiviral agents, which would be difficult to obtain via conventional routes.

The reaction of 1,3-dioxolanes has also been extended to 4-oxa analogues, to yield iodomethoxyacetic acid silyl ester derivatives.[118]

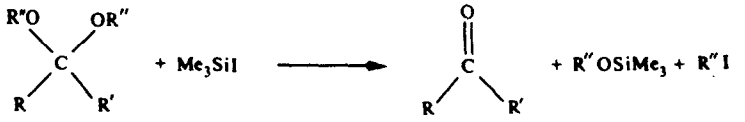


This bifunctional ether ester has been used as a starting material in the synthesis of hemithioacetals by alkylation of thiols. The hemithioacetals are useful precursors for the synthesis of cleavable cross linking reagents for proteins.

The conversion of acetals to aldehydes and ketones is usually achieved by treatment with aqueous acid. Under certain circumstances, it would be highly desirable to achieve this transformation under strictly neutral conditions. Iodotrimethylsilane can be used to convert acetals to the corresponding carbonyl compounds in very high yield[119] (Table 28).

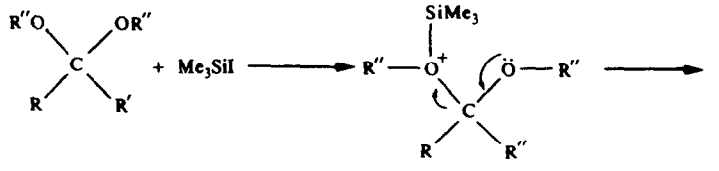
Table 28. Conversion of ketals into ketones with Me_3SiI

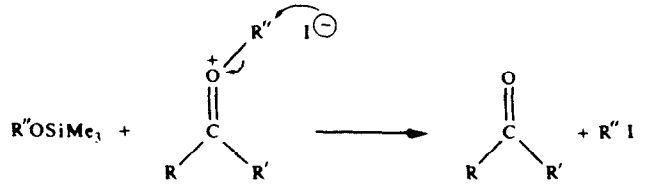
KETALS				YIELD (%)	
R	R'	R''	Solvent	NMR	Isolated
CH_3	CH_3	CH_3	CCl_4	> 95	--
$-(CH_2)_4$	-	CH_3	$CHCl_3$/propene	> 95	87
$-(CH_2)_5$	-	CH_3	$CHCl_3$/propene	> 95	90
C_6H_{13}	CH_3	CH_3	CH_2Cl_2	> 95	87
C_5H_{11}	H	CH_3	$CHCl_3$/propene	> 95	85
Ph	Ph	CH_3	$CHCl_3$/propene	> 95	98
$-(CH_2)_5$	-	CH_2CH_3	$CHCl_3$/propene	> 95	84
$-(CH_2)_5$	-	$-CH_2CH_2-$	CH_2Cl_2	~ 20	--



The reaction is carried out in the presence of propene to remove traces of HI, always present in iodotrimethylsilane.

In analogy with the reaction of ethers, the mechanism can be formulated as:





The reaction is however limited to dimethyl and diethyl acetals. Ethylene ketals gave complex mixtures of products. Ethylenedithioacetals could not be cleaved under the reaction conditions. This is not surprising since silicon forms a very weak bond with sulfur but a strong bond with oxygen.

It is interesting to note that orthoformates yield carboxylic esters on treatment with iodotrimethylsilane.

$$HC(OMe)_3 + Me_3SiI \longrightarrow H-\overset{\overset{O}{\|}}{C}-O-Me + MeOSiMe_3 + MeI$$

Alcohols

In the preceeding discussion of the reaction of ethers and acetals with iodotrimethylsilane, the reaction of intermediate silyl ethers with excess iodotrimethylsilane was shown to yield alkyl iodides.[93,120-122] These observations have been applied to the synthesis of alkyl iodides from the corresponding alcohols by reaction with iodotrimethylsilane[123] (Table 29).

Table 29. Conversion of alcohols into iodides with iodotrimethylsilane

STARTING ALCOHOL		PRODUCTS AND YIELDS	
R	Time(hr)	via Alcohol	via Silyl Ether
CH_3	0.5	100	--
CH_3CH_2	5	99	--
$(CH_3)_2CH$	24	96	--
$(CH_3)_3C$	0.2	100	--
cyclopentyl	0.4	100	--
$CH_3(CH_2)_3CHCH_2CH_3$	2	100	--
$n\text{-}C_{15}H_{31}CH_2$	24	88	79
$n\text{-}C_{11}H_{23}CH_2$	24	76	81
$n\text{-}C_9H_{19}CH_2$	24	73	88
$PhCH_2$	24	85	67
$PhCH_2CH_2$	24	87	84
cyclohexyl	24	81	75
$CH_3(CH_2)_3\overset{\overset{CH_3}{|}}{C}CH_2CH_3$	24	63	76
$ClCH_2CH_2CH_2CH_2$	24	80	76
4-Me-cyclohexyl	24	84	80
dl-2-octyl	24	79	82
d-S-2-octyl	24	95	75
$CH_3CH(OH)CH_2CH_2CH_2OH$	24	75	--

$$R-OH + Me_3SiI \rightleftharpoons R-\overset{\overset{SiMe_3}{|}}{\overset{+}{O}}-H \xrightarrow[I^-]{S_N2} R-I + Me_3SiOH$$

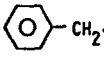
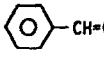
$$Me_3SiOH + Me_3SiI \longrightarrow (Me_3Si)_2O + HI$$

Silyl ethers can also be used for this purpose, as was initially demonstrated by Voronkov *et al.*[93,120-122] This eliminates the formation of HI in the reaction. These observations were later applied by Jung *et al.*[123]

$$R-O-SiMe_3 + Me_3SiI \longrightarrow RI + (Me_3Si)_2O$$

The reaction is general for primary, secondary and tertiary alcohols. Optically pure (+)-2-octanol was converted to (−)-2-octyl iodide with 94% inversion. Thus the silylated oxonium ion reacts with iodide via an S_N2 type mechanism.

Table 30. Conversion of alcohols to iodides with chlorotrimethylsilane/sodium iodide reagent

Alcohol (1)	1 : 2 : 3	Reaction Conditions Time /Temp. (min.)/(°C)	Yield of Iodide
	1: 2: 2	30/25	78
	1: 2: 2	40/25	98
	1: 2: 2	30/25	98
$1\text{-}C_9H_{19}$-	1: 2: 2	60/25	83
$2\text{-}C_9H_{19}$-	1: 2: 2	40/25	80
1-adamantyl	1: 2: 2	40/25	85
	1: 2: 2	20/25	98
	1: 2: 2	20/25	93
cholesterol	1: 2: 3	2hr./25	80

When alcohols are reacted with chlorotrimethylsilane/sodium iodide in acetonitrile solution, the corresponding alkyl iodides are obtained in high yield (Table 30).

The reaction with chlorotrimethylsilane/sodium iodide is rapid compared to that with iodotrimethylsilane. This is probably due to the use of a larger excess of the reagent. The reaction with iodotrimethylsilane can be accelerated not only be using excess of the reagent, but also by using added sodium iodide. Alcohols can be converted to alkyl iodides with hexamethyldisilane/iodine also.

The facile reaction of alcohols and ethers with iodotrimethylsilane to form iodoalkanes and their easy dehalogenation with zinc[124] has been combined into a simple and convenient one pot procedure for deoxygenation of alcohols and ethers (Table 31).[125]

$$R^1\text{—}O\text{—}R^2 \xrightarrow[2.\ Zn/AcOH/Me_3CN]{1.\ Me_3SiCl/NaI/Me_3CN} R^1\text{–}H$$

R^1 = Alkyl

R^2 = H, Alkyl, Me_3Si

The addition of a little acetic acid in the reduction step dramatically improves the product yield. The present procedure is very convenient, producing only hexamethyldisiloxane as the by product. Although alcohols can be deoxygenated by a variety of other methods, there is no other satisfactory method available for the conversion of ethers to alkanes. The deoxygenation of ethers is very efficient with the chlorotrimethylsilane/sodium iodide/zinc reagent system.

Although alcohols usually react with iodotrimethylsilane to yield alkyl iodides, the reaction can be stopped at the silyl ether stage in a interesting modification of the reagent system. Sakurai *et al.*[126] have observed that alcohols and carboxylic acids can be protected as their O-silyl derivatives by reaction with allyltrimethylsilane in the presence of iodotrimethylsilane. Iodine can be used in place of iodotrimethylsilane, thus exploiting the *in situ* generation of iodotrimethylsilane (Table 32).

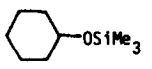
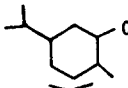
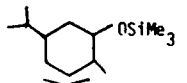
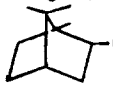
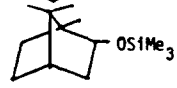
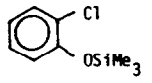
$$Me_3SiCH_2\text{—}CH{=}CH_2 + ROH \xrightarrow{I_2 \text{ or } Me_3SiI} R\text{—}O\text{—}SiMe_3 + Me\text{—}CH{=}CH_2$$

The silylation is possible only for primary and secondary alcohols. Tertiary alcohols undergo the

Table 31. Deoxygenation of alcohols and ethers into alkanes

Substrate R^1	R^2	Reaction 1		Reaction 2		Yield [%]
		Temp. [°C]	Time [h]	Zn (equiv.)	Time [h]	
$n\text{-}C_{10}H_{21}$	H	30-35°	1.0	3	6.0	80
$n\text{-}C_{10}H_{21}$	H	30-35°	1.0	7	6.0	86
$n\text{-}C_{12}H_{25}$	H	30-35°	1.0	7	5.0	93
$s\text{-}C_9H_{19}$	H	40-45°	1.5	7	6.0	61
4-t-butylcyclohexyl (cis and trans)	H	50-55°	2.5	7	5.0	40
$4\text{-}H_3CO\text{-}C_6H_4\text{-}CH_2$	H	30-35°	0.5	7	5.0	83
$(C_6H_5)_2CH$	H	30-35°	0.5	7	4.0	91
$n\text{-}C_{10}H_{21}$	CH_3	70-75°	1.5	7	4.5	82
$s\text{-}C_9H_{19}$	CH_3	70-75°	1.5	7	5.0	64
$n\text{-}C_{10}H_{21}$	$Si(CH_3)_3$	70-75°	1.0	6	4.0	82
$4\text{-}H_3CO\ C_6H_4\text{-}CH_2$	$Si(CH_3)_3$	50-55°	0.5	6	5.0	81
$(C_6H_5)_2CH$	$Si(CH_3)_3$	50-55°	0.3	6	4.0	85

Table 32. Conversion of alcohols, phenols, and carboxylic acids into silyl derivatives with allylsilanes catalyzed by iodine

Starting compound	Allylsilane	Conditions Temp/ C(time/h)	Silyl ether	Yield(%)
$ClCH_2CH_2OH$	$Me_3SiCH_2CH{=}CH$ (1a)	60 (0.5)	$ClCH_2CH_2OSiMe_3$	93
$n\text{-}C_4H_9OH$	$t\text{-}BuMe_2SiCH_2CH{=}CH$	70 (1)	$n\text{-}C_4H_9OSiMe_2\text{-}t\text{-}Bu$	90
$i\text{-}C_4H_9OH$	$Et_3SiCH_2CH{=}CH_2$	60 (0.5)	$i\text{-}C_4H_9OSiEt_3$	93
$HO(CH_2)_4OH$	1a	60 (2)	$Me_3SiO(CH_2)_4OSiMe_3$	83
$n\text{-}C_8H_{17}OH$	1a	40 (1)	$n\text{-}C_8H_{17}OSiMe_3$	95
$sec\text{-}C_8H_{17}OH$ (6b)	1a	60 (2)	$sec\text{-}C_8H_{17}OSiMe_3$	90
	1a	30 (1)		93
	1a	60 (1)		93
	1a	60 (1)		94
$PhCH_2OH$	1a	40 (2)	$PhCH_2OSiMe_3$	92
	1a	60 (0.5)		95
$n\text{-}C_5H_{11}CO_2H$	1a	60 (0.5)	$n\text{-}C_5H_{11}CO_2SiMe_3$	87

more familiar reaction to yield alkyl iodides, thus retarding the catalytic cycle shown below.

$$Me_3SiCH_2—CH=CH_2 + I_2 \longrightarrow Me_3SiI + CH_2=CH—CH_2—I$$

$$Me_3SiI + R—O—H \longrightarrow R—O—SiMe_3 + HI$$

$$HI + Me_3SiCH_2—CH=CH_2 \longrightarrow [Me_3SiCH_2—\overset{+}{C}H—CH_3]I^-$$

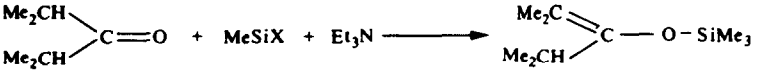
$$(Me_3SiCH_2—\overset{+}{C}HCH_3]I^- + ROH \underset{\text{or}}{\longrightarrow} R—O—SiMe_3 + Me—CH=CH_2 + HI$$

$$[Me_3SiCH_2—\overset{+}{C}H—CH_3]I^- \longrightarrow Me_3SiI + Me—CH=CH_2$$

Other substituted allylsilanes can also be used for this reaction. Iodine and iodotrimethylsilane can be substituted by bromine and bromotrimethylsilane, although higher reaction temperatures are required. This procedure is reminiscent of the silylation of –OH and –SH groups by allyltrimethylsilane in the presence of p-toluenesulfonic acid or trifluoromethanesulfonic acid as catalysts.

Carbonyl compounds

Because of the lability of the silicon-iodine bond, iodotrimethylsilane can be used for O-silylation of carbonyl compounds. Simchen *et al.*[127] compared various silylating agents for the synthesis of enol silyl ethers from diisopropylketone.



The order of reactivity for different silylating agents was found to be

$$x = I > CF_3SO_3 > Br > CF_3CH_2SO_3 \gg Me_3SiOSO_3 > CH_3SO_3 > Cl$$

Iodotrimethylsilane was found to be the most reactive reagent among a variety of reagents including trimethylsilyl trifluoromethanesulfonate. Trimethylsilyl enol ethers are important intermediates in organic synthesis. They are used for the preparation of α-functionalised carbonyl compounds by reaction with electrophiles,[1] for the preparation of α,β-unsaturated compounds and above all for directed aldol condensations. There are many reagents available for the synthesis of kinetic enolates, but the generation of thermodynamically equilibrated mixture of enol silyl ethers from unsymmetrical ketones often requires harsh conditions or inconvenient procedures.

Miller *et al.*[128] have discovered that iodotrimethylsilane in conjunction with hexamethyldisilazane can be used to prepare enol silyl ethers in high yield at room temperature (Table 33). These exceedingly mild conditions lead to thermodynamically equilibrated products and is applicable to ketones, aldehydes and enones. Esters were not affected under the reaction conditions.

The reactions take different course when the base is omitted. Thus, Schmidt *et al.*[18,129] discovered that treatment of ketones containing an α-CH_2 or-CH_3 group with chlorotrimethylsilane/sodium iodide in acetonitrile results in condensation to yield β-haloketones. The reactions have been postulated to proceed via the 1 iodo-1-trimethylsilyloxy adducts formed by 1,2-addition of iodotrimethylsilane to the carbonyl group.

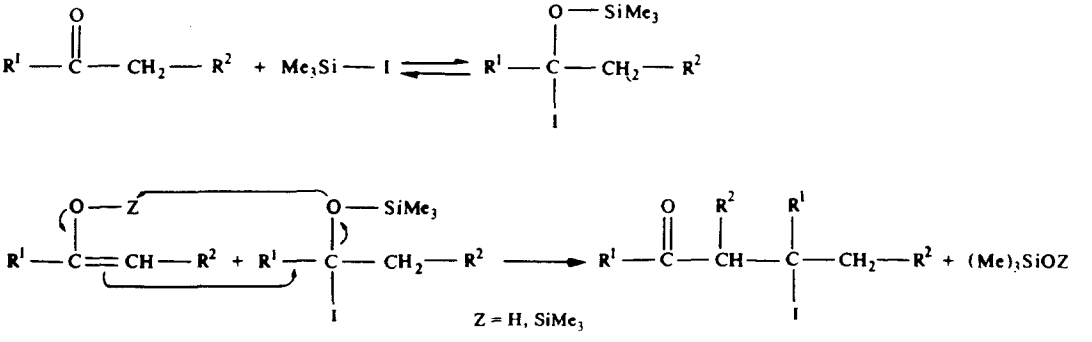
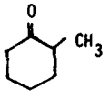
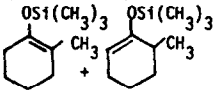
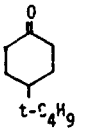
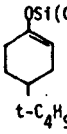
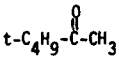
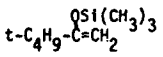
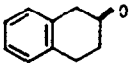
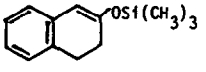
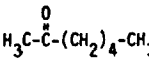
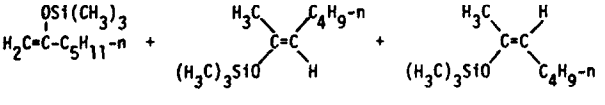
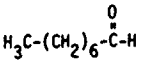
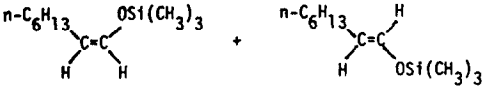
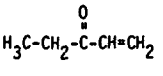
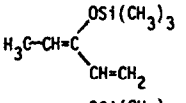
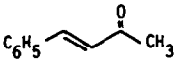
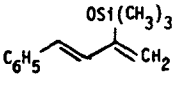
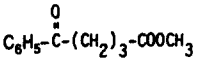
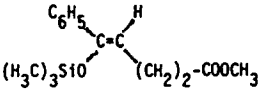
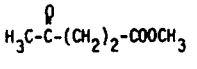
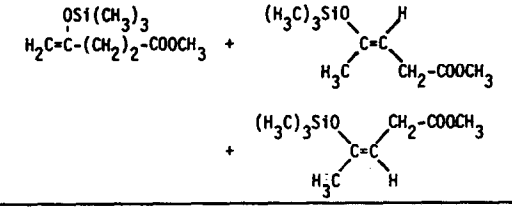
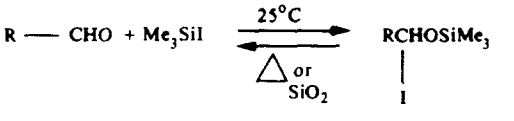


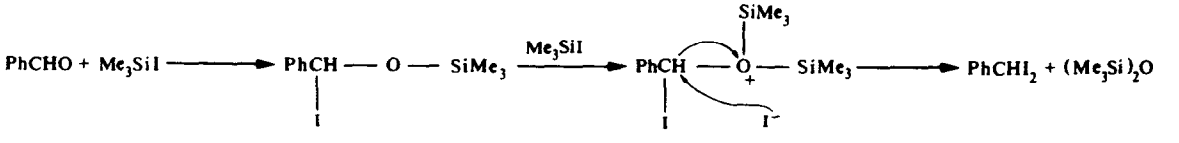
Table 33. Preparation of trimethylsilylenol ethers

Carbonyl Compound	Product(s)	Reaction Conditions	Product distribution	Yield [%]
		1. -10°/0.3h 2. 25°/2h	90:10	90
		1. -10°/0.5h 2. 25°/2h	---	95
		1. -10°/0.5h 2. 25°/3h	---	98
		1. -10°/0.3h 2. 25°/2h	---	95
		1. -10°/0.5h 2. 25°/2h	8:25:64	92
		1. -20°/0.3h 2. 25°/2h	77:23	89
		1. -20°/0.3h 2. 25°/2h	---	89
		1. -10°/0.3h 2. 25°/1h	---	91
		1. -20°/0.2h 2. 25°/8h	---	96
		1. -20°/0.2h 2. 25°/10h	12:20:68	95

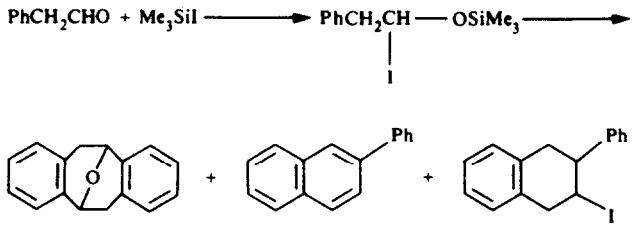
The formation of such halosilyloxy adducts from aldehydes and iodotrimethylsilane was demonstrated by Jung *et al.*[130]



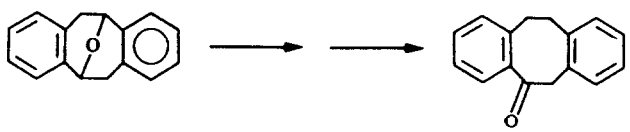
When benzaldehyde was treated with iodotrimethylsilane, α,α-diiodotoluene was obtained via the intermediate iodoether.



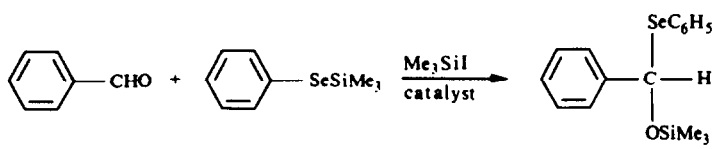
The second step is analogous to the reaction of silyl ethers with iodotrimethylsilane. The α,α-diiodotoluene decomposes readily during the work up procedure. When phenylacetaldehyde was treated with iodotrimethylsilane, a mixture of products was obtained.



The ether was converted in two steps, into dibenzocyclo-octadienone, an important starting material for the synthesis of certain biologically active compounds.



Detty[15] has observed the Me_3SiI-catalysed 1,2 and 1,4 additions of phenylselenotrimethylsilane to various carbonyl compounds in analogy with the formation of 1-iodo-1-silyloxyalkanes with iodotrimethylsilane itself, e.g.:



α-Hydroxyketones are deoxygenated by iodotrimethylsilane in a very facile reaction (Table 34) thus providing an easy synthesis of deoxybenzoins.[131] The reaction can be visualised to proceed via the formation of α-iodoketones, in analogy with the reaction of alcohols with iodotrimethylsilane to yield alkyl iodides.

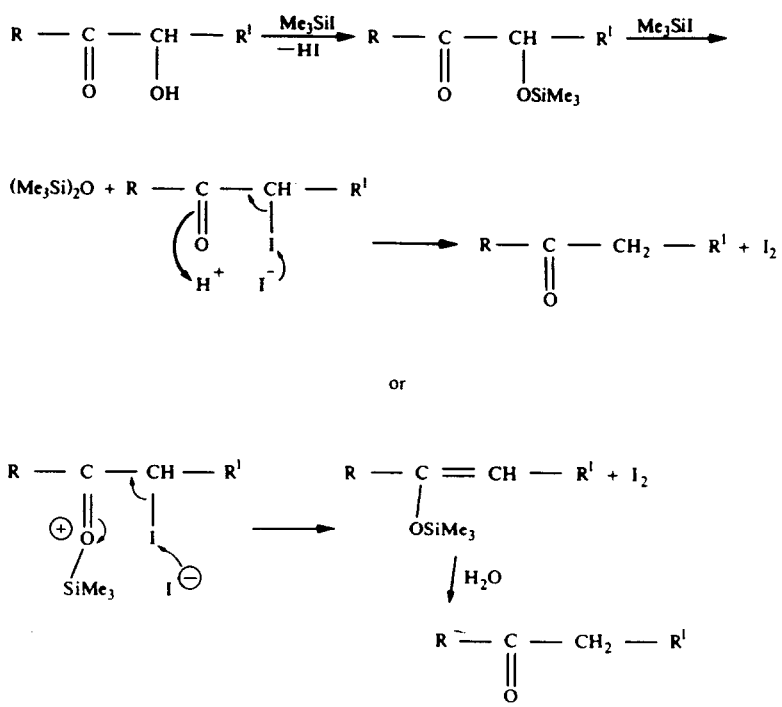
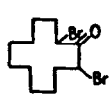
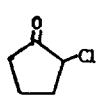
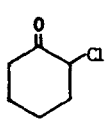
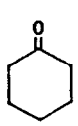


Table 34. Reduction of α-ketols with iodotrimethylsilane

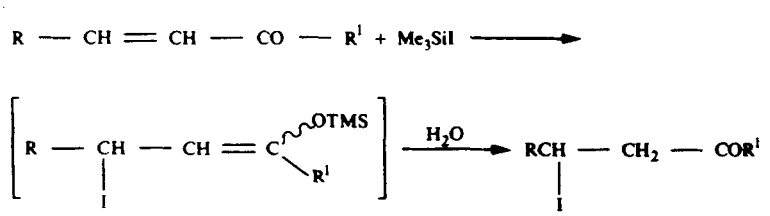
α-Ketol	Ketone Yield, %
Benzoin	95
Toluoin	92
p-Anisoin	87
Piperoin	82
Butyroin	90
Isobutyroin	76

The intermediacy of α-haloketones in the reduction of α-hydroxyketones was demonstrated by treating α-haloketones with chlorotrimethylsilane/sodium iodide in acetonitrile, when the corresponding dehalogenated ketones were obtained in very high yield (Table 35).[132]

Table 35. Reduction of α-haloketones with sodium iodide/chlorotrimethylsilane

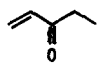
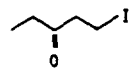
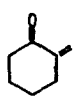
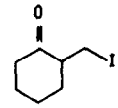
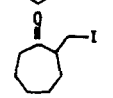
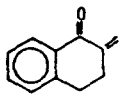
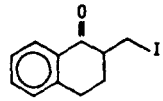
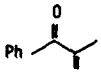
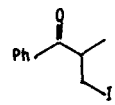
substrate	ketone	amounts (mmol) of reagents substrate: $ClSi(CH_3)_3$: NaI			reaction time/temp. (hr)	yield[%]
$Ph-\overset{O}{\overset{\|}{C}}-CH_2Br$	$Ph-\overset{O}{\overset{\|}{C}}-CH_3$	10:	15:	15	5/r.t.	91
$Ph\overset{O}{\overset{\|}{C}}CHBrPh$	$Ph\overset{O}{\overset{\|}{C}}CH_2Ph$	10:	15:	15	3/r.t.	94
$Ph\overset{O}{\overset{\|}{C}}CH_2Cl$	$Ph\overset{O}{\overset{\|}{C}}CH_3$	10:	15:	15	4/r.t.	89
$p\text{-}Ph\text{-}Ph\overset{O}{\overset{\|}{C}}CH_2Br$	$p\text{-}Ph\text{-}Ph\overset{O}{\overset{\|}{C}}CH_3$	10:	15:	15	3/r.t.	93
		10:	40:	60	12/r.t. 2/reflux	98 98
		10:	20:	30	48/r.t. 3/reflux	75 78
		10:	20:	30	48/r.t. 3/reflux	72 78

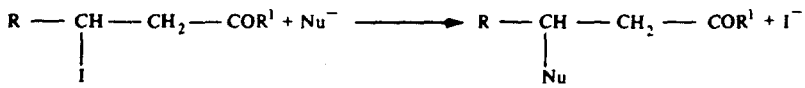
When α,β-unsaturated ketones are treated with iodotrimethylsilane, 1,4-adducts (Michael addition) are formed in high yield.[133]



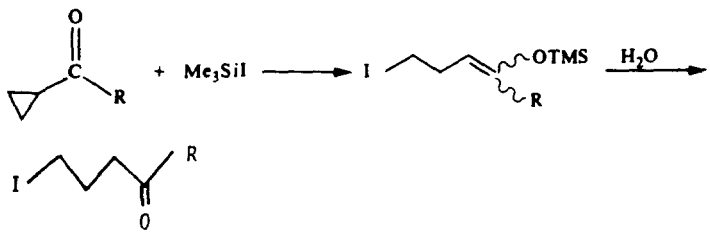
The adducts react with water to yield β-iodoketones, which are synthetically very useful (Table 36). The β-iodoketones could be transformed further into other compounds by nucleophilic displacement of the iodide.

Table 36. Michael addition of iodotrimethylsilane to α,β-unsaturated ketones

Enone	Reaction Conditions	Product	Yield (%)
	-40°, 1h		85
	-78°, 0.5h		81
	-40°, 0.5h		85
	-40°, 0.5h		75
	-40°, 1h		80
	-20°, 2h 25°, 2h		93



These observations have been further extended by Miller *et al.* to cyclopropyl ketones, yielding γ-iodoketones by cleavage of the cyclopropyl ring.[133,134]



The ring opening proceeds under very mild conditions and the γ-iodoketones are obtained in high yield upon aqeous workup (Table 37).

The reaction usually proceeds with high regioselectivity resulting in cleavage of the cyclopropane bond with the best overlap with the π-orbitals of the carbonyl group. The intermediate silyl ethers can be isolated when the reaction is performed in the presence of a hindered base and the hydrolytic workup is avoided. The electrophilic ring opening of cyclopropyl ketones has applications in the synthesis of natural products. The yields and regioselectivity obtained by cleavage of cyclopropyl ketones with iodotrimethylsilane under mild and neutral conditions, are a significant improvement over the usual acidic reagents employed for this reaction.[135]

When sterically strained cyclobutanones are treated with iodotrimethylsilane in the presence of ZnI_2 or Hg–H_2O, the cyclobutyl ring is cleaved, resulting in the formation of β-iodoketones in high yield (Table 38).[136] The reaction shows high regioselectivity. Because of the easy synthesis of cyclobutanones from olefins and ketones via [2+2]cycloaddition, this sequence of reactions represents a cyclic homologation of a cyclic olefin to a β-functionalised cyclic ketone, e.g.:

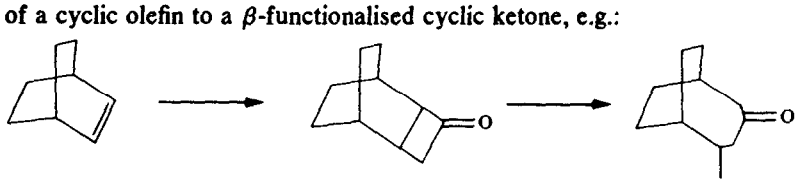


Table 37. Ring opening of cyclopropylketones with iodotrimethylsilane

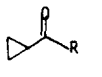
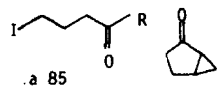
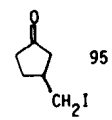
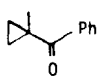
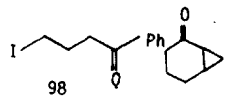
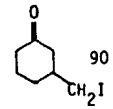
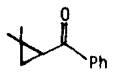
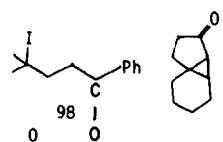
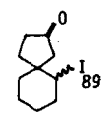
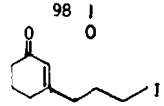
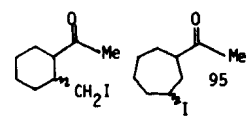
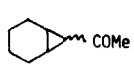
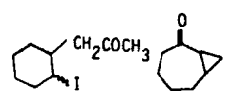
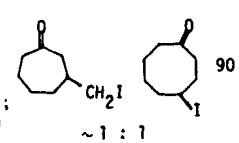
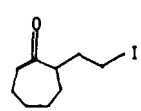
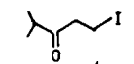
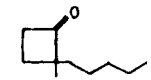
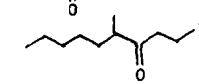
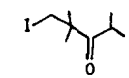
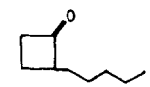
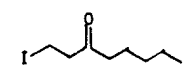
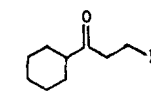
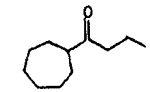
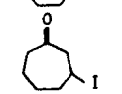
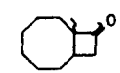
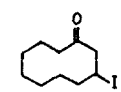
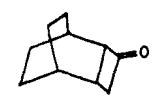
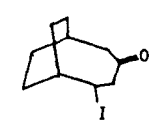
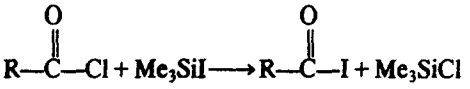
Reactant	Conditions	Product [total yield, %]	Conditions	Products [total Yield, %]
 a, R=Me b, R=Ph	-20 °C, 0.5h; 25 °C, 2h	 a 85 b 88	-20°C, 0.5h	 95
	-10 °C, 1h; 25 °C, 1h	 98	0°C, 1h; 25 °C, 2h	 90
	25 °C, 2h	 98	-20°C, 0.5h	 89
	-5 °C, 1h; 25 °C, 1h	 98	-10°C, 1h; 25°C, 2h	 95 9 : 1
	-10 °C, 1h; 25° , 2h	 94	-10°C, 1h; 25°C, 2h	 90 ~1 : 1
	-10 °C, 1h; 25 °C, 2h	 96		

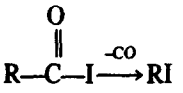
Table 38. Ring opening of cyclobutanes with iodotrimethylsilane

Ketone	Conditions	Product	Yield (%)
	24°, 6h		83
	24°, 16h		82
	24°, 4h		75
	24°, 7h		72
	24°, 16h		78
	24°, 9h		88
	24°, 5h		85
	24°, 18h		95
	24°,21h		81

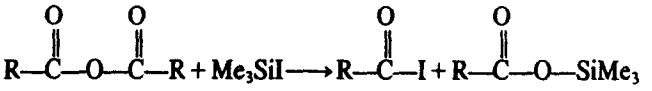
Finally, acyl halides react with iodotrimethylsilane or hexamethyldisilane/iodine to yield the corresponding acyl iodides via a halogen exchange reaction (Table 39).[137] This method provides easy access to unstable acyl iodides in high yield with only chlorotrimethylsilane as the by product, which can be removed from the reaction mixture under reduced pressure.



We have previously mentioned[49] that in case of tertiary alkylacyl halides, decarbonylation takes place at high temperature to yield the corresponding t-alkyl iodides.



The reaction of anhydrides with iodotrimethylsilane is limited to straight chain primary alkylcarboxylic acids.[49]

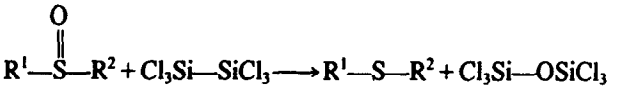


$R = CH_3,\ CH_3—CH_2,\ CH_3—CH_2—CH_2$

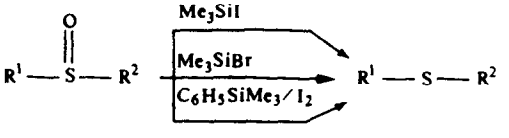
No reaction was observed with chloroformates, RO.CO.Cl.

Sulfoxides and sulfonyl halides

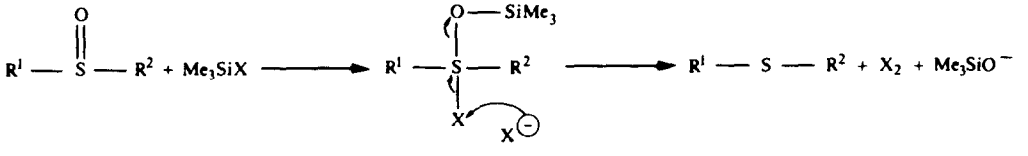
Deoxygenation of sulfoxides to sulfides is an important synthetic transformation in organic chemistry. A variety of methods are available for the synthesis of sulfides from sulfoxides.[138] Because of the high affinity of silicon for oxygen, hexachlorodisilane has proved to be an effective reagent.[139]



Sulfoxides are deoxygenated under mild conditions by iodotrimethylsilane bromotrimethylsilane and phenyltrimethylsilane/iodine to the corresponding sulfides in high yield (Table 40).[140]

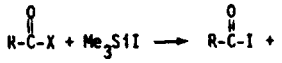


Iodotrimethylsilane reacted much more vigorously than bromotrimethylsilane. Deoxygenations with phenyltrimethylsilane/iodine were carried out at 120°. The reaction mechanism probably involves the formation of a tetracoordinate intermediate, followed by nucleophilic attack by the halide ion to yield the desired sulfide.



In some cases, halogenated by-products were obtained probably by 1,2-elimination followed by the reaction with the halide. When the chlorotrimethylsilane/sodium iodide is used for deoxygenation of

Table 39. Conversion of acyl chlorides to acyl iodides



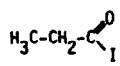
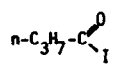
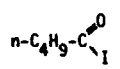
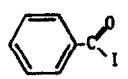
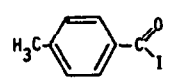
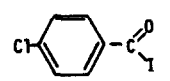
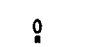
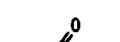
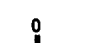
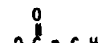
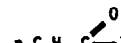
X	Product	Yield [%]
Cl		46
Cl		93
Cl		92
Cl		93
Cl		86
Cl		61
Cl		78
		100
		100
		100

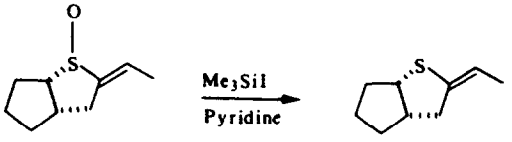
Table 40. Deoxygenation of sulfoxides R^1R^2SO with Me_3SiI, Me_3SiBr and $PhSiMe_3$–I_2 reagents

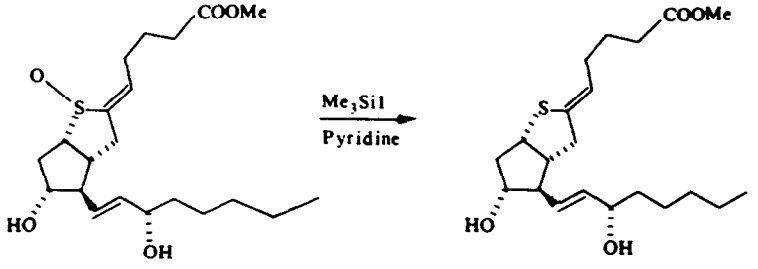
	R^1	R^2	Time/°C	Yield Sulfide (%)
Me_3SiI	Me	Me	20 min /room temp	~50[c]
	nC_3H_7	nC_3H_7	"	72
	nC_4H_9	nC_4H_9	"	82
	$-(CH_2)_4-$		"	91
	C_6H_5	C_6H_5	2 hrs/room temp	73
	$C_6H_5CH_2$	$C_6H_5CH_2$	20 min /room temp	mixture of products
Me_3SiBr	Me	Me	30 min /room temp	~50
	nC_3H_7	nC_3H_7	"	79
	nC_4H_9	nC_4H_9	"	82
	$-(CH_2)_4-$		"	85
	C_6H_5	C_6H_5	2 days/refluxing	mixture of products
	$C_6H_5CH_2$	$C_6H_5CH_2$	"	mixture of products
$PhSiMe_3$-I_2	nC_3H_7	nC_3H_7	6 hr/120-30°C	80
	nC_4H_9	nC_4H_9	"	87
	C_6H_5	C_6H_5	8 hrs/120-30°C	83
	$C_6H_5CH_2$	$C_6H_5CH_2$	6 hrs/120-30°C	81

Table 41. Deoxygenation of sulfoxides with chlorotrimethylsilane-sodium iodide reagent

Substrate	Reagent Amounts (mmol) S:$ClSiMe_3$:NaI	Reaction Time	Yield (%) of Sulfide
$(CH_3)_2SO$	10:15:30	10 min.	52
$(n\text{-}C_3H_7)_2SO$	10:15:30	10 min.	78
$(n\text{-}C_4H_9)_2SO$	10:15:30	10 min.	90
	10:15:30	10 min.	83
$(C_6H_5CH_2)_2SO$	10:30:40	40 min.	91
$(C_6H_5)_2SO$	10:15:30	20 min.	95
$(Cl\text{-}C_6H_4)_2SO$	10:15:30	20 min.	95
$(CH_3\text{-}C_6H_4)_2SO$	10:15:30	20 min.	96

sulfoxides, the reaction proceeds faster as the amount of iodide is increased (Table 41).[141] These results support the second step of the mechanism proposed above. Iodide catalysis has also been observed with other deoxygenating agents. Hexamethyldisilane/iodine reagent has also been used for the synthesis of sulfides from sulfoxides. The mildness of the reaction conditions for deoxygenation of sulfoxides with iodotrimethylsilane and its *in situ* equivalents has been exploited by Nicolaou *et al.*[142] in the synthesis of biologically important thiaprostacyclins.





The reduction is highly selective, the alcohol and ester functions remaining intact during the course of this reaction.

Sulfones do not react with iodotrimethylsilane, presumably due to the lower nucleophilicity of the sulfone oxygen compared to the sulfoxide oxygen. On the other hand, sulfonyl halides react very readily with iodotrimethylsilane and its *in situ* equivalents to yield the corresponding disulfides in excellent yield (Table 42).[143]

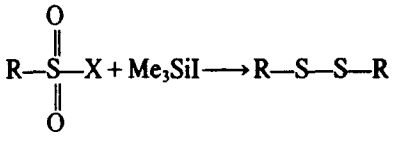
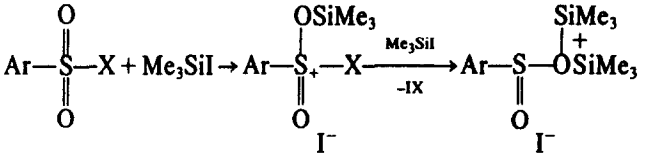
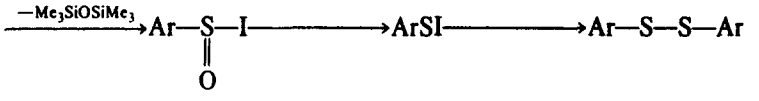


Table 42. Reductive coupling of sulfonyl, sulfinyl and sulfenyl derivatives to disulfides with iodotrimethylsilane

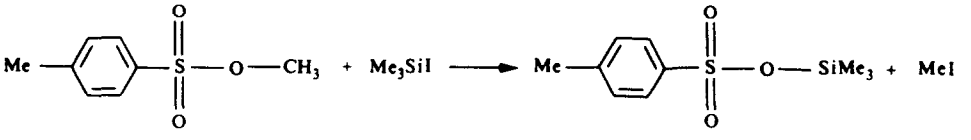
SUBSTRATE	Disulfide Yield (%)
CH_3SO_2Cl	100
$CH_3CH_2SO_2Cl$	80
$C_6H_5CH_2SO_2Cl$	98
$C_6H_5SO_2Cl$	100
p-$CH_3C_6H_4SO_2Cl$	89
p-$CH_3C_6H_4SO_2Br$	90
p-$BrC_6H_4SO_2Cl$	86
p-$MeC_6H_4SO_2Cl$	79
p-$BrC_6H_4SO_2Cl$	80
p-$ClC_6H_4SO_2Cl$	100
p-F $C_6H_4SO_2Cl$	90
p-F C_6H_4SOCl	96
p- C_6H_4SCl	88
p-$CH_3C_6H_4SO_2Na$	75
p-F $C_6H_4SO_2Me$	89

Aryl and aralkylsulfonyl chlorides and bromides react rapidly with iodotrimethylsilane at room temperature, whereas alkylsulfonyl halides are reduced at 81°. The following mechanism has been proposed.





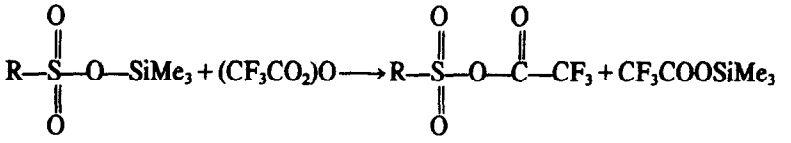
The reductive dimerisation is also applicable to sulfinic acids, sulfinic acid salts, sulfinyl chlorides, and sulfenyl chlorides. Sulfonyl fluorides, sulfonic acids, their salts, and esters are not reduced under the reaction conditions. It should be noted however, that methyl p-toluenesulfonate was dealkylated very efficiently by iodotrimethylsilane.



Shipov *et al.*[144] have used this reaction for the synthesis of various trimethylsilyl sulfonates.

R = methyl, n-butyl, phenyl, etc

The trimethylsilyl sulfonates can be used for the synthesis of mixed anhydrides.



During the course of this research on the reductive dimerisation of sulfonyl halides, a phase transfer catalysis method was developed for the *in situ* generation of iodotrimethylsilane equivalents. The reactions were carried out with chlorotrimethylsilane/sodium iodide in dichloromethane or chloroform in the presence of tetra-n-butylammonium iodide as a phase transfer catalyst. Crown ethers cannot be used because of the facile cleavage of ethers with iodotrimethylsilane.

Amines

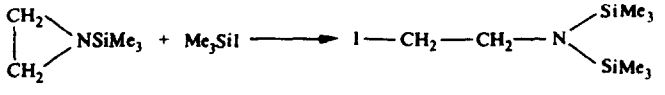
Iodotrimethylsilane forms adducts with amines. Recently, adducts with quinoline and DABCO have been used for the demethylation of methyl ethers. The formation of an initial adduct with the dimethylamino group has also been proposed during the synthesis of α-methylene-γ-butyrolactones. The reaction of lithium or sodium bis(trimethylsilyl)amide with iodotrimethylsilane has been used to prepare tris(trimethylsilyl)amine.[145]

$$(Me_3Si)_2NM + Me_3SiI \longrightarrow (Me_3Si)_3N + MI$$

$$M = Li,\ Na$$

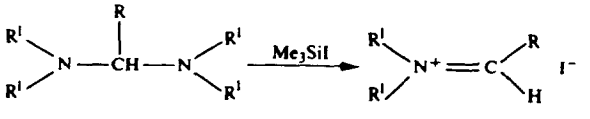
The reaction is carried out at room temperature, thus offering a distinct advantage over the corresponding reaction with chlorotrimethylsilane, which requires 8–10 h in refluxing benzene.

When N-trimethylsilylaziridine is treated with iodotrimethylsilane, N-β-iodoethyl-N,N-bis(trimethylsilyl)amine is formed spontaneously in 94% yield.[146]



The product can be used for the introduction of aminoethyl groups into organic and organosilicon compounds. The ring opening of aziridines is reminiscent of the ring opening of epoxides with iodotrimethylsilane.

The reaction of iodotrimethylsilane with 1,1-diaminoalkanes has important synthetic applications. Reaction with N,N-tetraalkyldiaminoalkanes yields the corresponding Mannich salts in very high yields.[147]



$R = H \quad R^1 = Me$

$R = Et \quad R^1, R^1 = -(CH_2)_5-$

$R = Pr^i \quad R^1 = Bu^n$

N,N-Dimethyl(methylene) immonium iodide (R=H, R^1=CH_3) has found extensive use in organic synthesis by Eschenmoser *et al.*[148] and other groups.[149] These Mannich salts react with many nucleophiles like Grignard reagents, vinyl-lithium reagents, thiophenoxides, and many stabilised carbanions to yield synthetically useful intermediates.

Alkyl halides

As so far discussed, all the reactions of iodotrimethylsilane have involved bonding of silicon to an

oxygen or nitrogen atom. Iodotrimethylsilane, as shown, undergoes halogen exchange with benzyl chloride and bromide.[150]

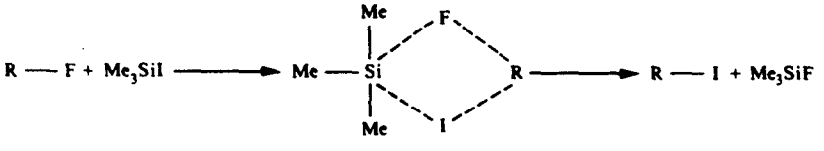
$$Me_3SiI + C_6H_5CH_2Cl \longrightarrow Me_3SiCl + C_6H_5CH_2I \qquad 100\%$$

The reaction was carried out at 50° in the presence of 5 mole % tetra-n-butylammonium chloride. In the absence of the catalyst, no reaction takes place even after an extended period of time. The corresponding reaction with benzyl bromide is reversible to a certain extent, so that a mixture of benzyl iodide and bromide (92:8) is produced under equilibrium conditions.

The reaction of iodotrimethylsilane with alkyl fluorides does not require any catalysis and is faster than with chlorides and bromides. Benzylic, secondary, and tertiary alkyl fluorides provide the corresponding iodoalkanes in very high yields (Table 43).[151]

Table 43. Synthesis of iodoalkanes. $RX + Me_3SiI \rightarrow RI + Me_3SiX$

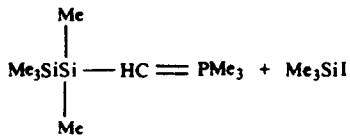
	Substrate	Reaction Conditions		Yield
X=	R=	Time (hr)	Temperature (°C)	(%)
F	1-Hexyl	48	25	81
F	1-Decyl	24	61	Mixture of Products
F	Benzyl	48	25	78
F	Cyclohexyl	16	25	72
F	1-Adamantyl	16	25	87
F	2-Norbornyl	48	25	76
Cl	1-Adamantyl	16	61	94
Cl	2-methyl-2-propyl	16	61	90

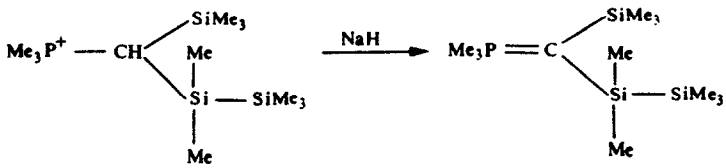


The halogen exchange reaction probably proceeds via an intermediate pentacoordinated silicon species. The fluoride–iodide halogen exchange can also be accomplished with chlorotrimethylsilane/sodium iodide or hexamethyldisilane/iodine. The reaction with primary fluoroalkanes is sluggish and generally leads to a mixture of iodoalkanes. Tertiary alkyl chlorides can also be converted to the corresponding iodides. The easy synthesis of fluoroalkanes from alkenes, alcohols and other precursors with HF or with HF/pyridine reagent,[152] make the present method an attractive route to iodoalkanes through the corresponding fluoroalkanes.

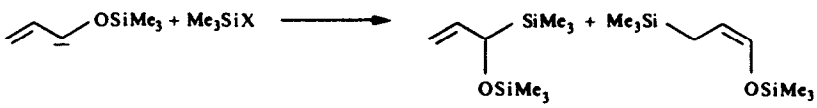
Carbanions

Iodotrimethylsilane has been used for the C-silylation of phosphonium ylids for the synthesis of silyl substituted derivatives.[153]



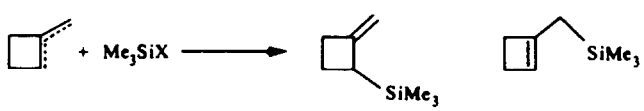


Iodotrimethylsilane has been used for the silylation of ambient carbanions to achieve different regioselectivity from that obtained with chlorotrimethylsilane and other silylating agents, e.g.[154]



X = F	35%	65%
X = Cl	50%	50%
X = Br	75%	25%
X = I	85%	15%

The regioselectivity thus changes depending upon the nature of the leaving group on silicon. Differing regioselectivity has also been observed in the silylation of the allylic carbanion derived from methylenecyclobutane.[155]

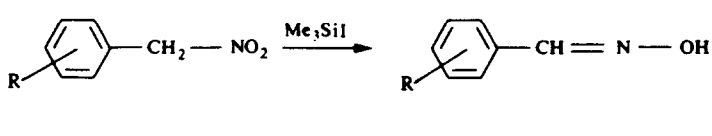


X = Cl, 25°	50	50
X = Cl, −78°	60	40
X = Br, 25°	25	75
X = I, 0°	25	75

These products have been converted to trimethylsilylisoprene, which is a useful terpene synthon.

Nitro and nitroso compounds

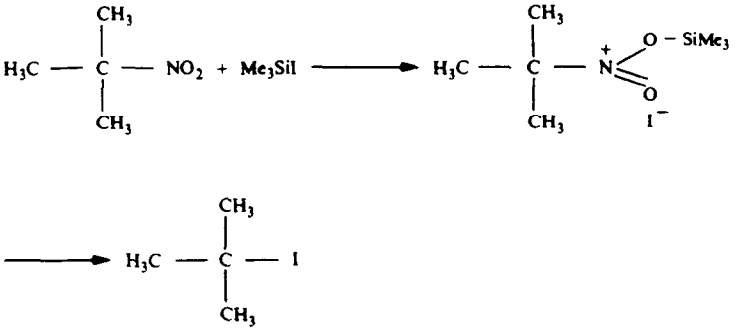
Nitro compounds react with iodotrimethylsilane via initial deoxygenation followed by dehydration in case of primary nitro alkanes.[156]



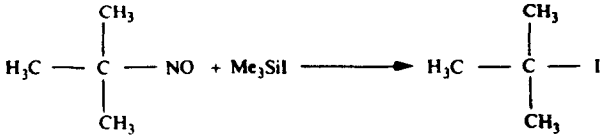
R = oMe, m — Me, p — Me, p — MeO

When the nitro group is attached to a tertiary alkyl center, immediate cleavage of the carbon–

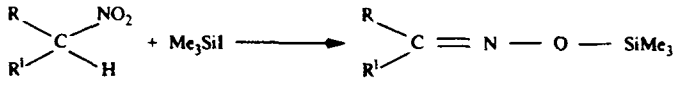
nitrogen bond is observed, resulting in the formation of t-alkyl iodide. t-Alkyl nitrosoalkanes react in a similar fashion.



The fate of the nitro group is not known, although large amounts of hexamethyldisiloxane are formed.

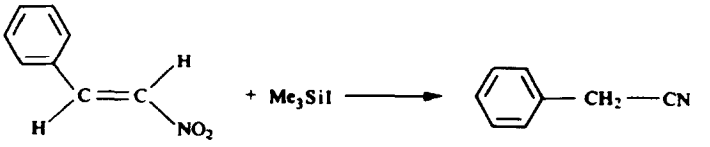


Secondary alkyl nitro compounds undergo selective deoxygenation to the corresponding oxime silyl ethers. No further reaction (reduction or Beckman rearrangement) is observed.



$R,R^1 = CH_3,\ CH_3;\ CH_3,\ C_2H_5;\ -(CH_2)_4;\ -(CH_2)_5$

Finally, when nitrostyrene was treated with iodotrimethylsilane, phenylacetonitrile was obtained in excellent yield.



The mechanism of these reactions are under investigation.

Since its introduction in 1976, iodotrimethylsilane became a widely used synthetic reagent. Iodotrimethylsilane a "hard–soft" reagent seems to be highly versatile for reaction with organic functional groups containing oxygen, nitrogen, fluorine and other nucleophilic centers capable of forming strong bonds with silicon. It is expected that its use, together with a number of convenient "*in situ*" preparations, will continue to expand and find many additional applications.

Acknowledgement—Support of our work on iodotrimethylsilane by the National Science Foundation and the National Institutes of Health is gratefully acknowledged. Dr. T. L. Ho in particular and other members of our research group contributed significantly to much of our work summarized in this review.

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$$Me_3SiI + I_2 \rightleftharpoons Me_3SiI_3$$

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