SILICON - APPLICATION TO ORGANIC SYNTHESIS

ANNUAL SURVEY COVERING THE YEAR 1973

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CONTENTS

I. GENERAL COMMENTS

In this first annual survey in which organosilicon is broken down into sections, it was considered desirable to group together applications of silicon chemistry to organic synthesis. The guiding principle is that the final reaction product not contain silicon, and that the reaction in question be synthetically useful, rather than produce a product which can be purchased from commercial sources with far less expense.

The papers in this survey are grouped by reaction type rather than by silicon reagent. As applications of organosilicon compounds are widely scattered in the literature and many are not specifically abstracted—over one-third of the references in this survey were undetected by two independent computerized information retrieval programs—the author would appreciate having re- or preprints of papers mentioning synthetic applications sent to him for inclusion in future surveys.

Specifically excluded from this survey are references to silylation as a derivitization procedure for chromatography or mass spectrometry (except where significant new techniques are presented), the use of silicone fluids and resins in coatings, stationary phases, and heat transfer media, and reports from the patent literature (which is unlikely to contain sufficient experimental detail to be applicable).

An excellent introduction to the use of organosilicon reagents in organic synthesis is the review by the late J. F. Klebe on "Silylation in Organic Synthesis" (1), which covers the literature through mid-1969 with heavy emphasis on silicon-nitrogen reagents.

The usual abbreviations for solvents and organic groups are employed—TMEDA = tetramethylethylene diamine, HMPT = hexamethylphosphortriamide, DME = dimethoxyethane, Pyr = pyridine, etc.

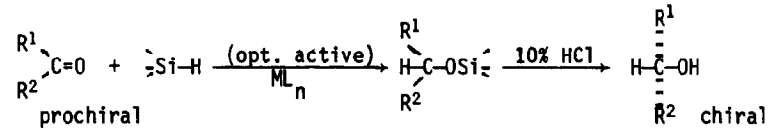
II. OXIDATION AND REDUCTION

Use of a commercially available siloxane, $Me_3SiO(MeHSiO)_{\sim 35}SiMe_3$, as a

reducing agent has been reviewed (2) with emphasis on the use of this reagent to generate Sn-H bonds in situ.

Hydrosilylation followed by hydrolysis for conversion of $R_2C{=}O$ to R_2CHOH functions continues to be an active area (3-7). Although most effort has been with Rh(I) complexes as catalysts, the ruthenium complex $(Ph_3P)_3RuCl_2$, in $7x10^{-3}$ molar proportion, catalyses the reduction of aldehydes and ketones by Et_3SiH to silyl ethers in 55-74% yield (8) but appears to be less effective than the cheaper $(Ph_3P)_3RhCl$.

Asymmetric reduction of ketones by hydrosilylation in the presence of a chiral catalyst has been reported by three groups (9-11) according to the genera scheme of eq. 1. Phenyldimethylsilane and trimethylsilane asymmetrically hydro-



(1)

silylate phenyl ketones under catalyst by the chiral (R)$(BzMePhP)_2RhH_2(solvent)_2$. Optical yields in the 30-60% range were found for the alcohols produced by acid hydrolysis of the $PhMe_2SiOR$ ethers. Surprisingly, t-butyrophenone (R^1= t-butyl, R^2= phenyl) gave alcohols of opposite configuration with different silanes: phenyldimethylsilane affording the (S) enantiomer in 62% optical yield and trimethylsilane the (R) alcohol in 28% optical yield (10).

Similar results using the commercially available (+)-diop (1,4-bis(diphenylphosphino)-2,3-dihydroxyethane) as a Rh(I) complex have been reported (11). Using naphthylphenylsilane, $NpPhSiH_2$, as the reductant, and the catalyst in a 1:50 molar ratio, acetophenone was converted in 58% optical yield to (S)-(−)-phenylmethylcarbinol. With isobutyrophenone, the best optical yield was realized with diphenylsilane as the hydrosilylating agent. It is cautioned that for maximum asymmetric induction, the silane and the ketone must be carefully matched. A resin-immobilized catalyst gave practically identical optical purities in the products, but appears to offer more novelty than practicality as it simplifies the reaction workup only marginally.

The (+)-diopRh(I) complex is also useful for the asymmetric hydrosilylation

of imines to amines (eq. 2)(12). Use of a polyhydrosiloxane (2) gives lower

$$R^1R^2C{=}N{-}R^3 \;+\; 2\ Ph_2SiH_2 \xrightarrow[\text{benzene}]{\text{(+)-diopRh(I)}} \xrightarrow{HCl,\text{water}} R^1R^2\overset{*}{C}H{-}NHR^3 \qquad (2)$$

$R^1{=}R^3{=}$ Ph, $R^2{=}$ Me 47% optical yield (S)

$R^1{=}R^3{=}$ $PhCH_2$, $R^2{=}$ Me 13% optical yield

optical yields, as does high reaction temperature. Indeed, the log of the optical yield exhibits a linear correlation with the inverse of the temperature. This reaction shows promise for effecting the speed-y conversion of ketones to pharmacologically active amines.

The generality of transition metal catalysed hydrosilylation as a superior, mild method for the reduction of Schiff bases under neutral non-aqueous conditions has been explored (13). The most effective systems were diethylsilane in benzene at room temperature with 0.5 mole% of tris(triphenylphosphine)rhodium(I)chloride or the cheaper combination of triethylsilane and palladium(II)chloride. As shown in eq. 3, the intermediate silyl amines can be acylated in good yield to amides, e.g. 1 → 2.

$$Ph{-}\underset{\displaystyle R^1}{\overset{|}{C}}{=}NR^2 \xrightarrow[\substack{Et_2SiH_2,\ PhH\\ 25^o,\ 1\ hr}]{(Ph_3P)_3RhCl} Ph{-}\underset{\displaystyle R^1}{\overset{H}{\overset{|}{C}}}{-}N{-}R^2 \quad (\underset{\displaystyle R^1}{\overset{H}{\overset{|}{C}}}{-}N{-}R^2 \;=\; \underset{\displaystyle R^1}{\overset{H}{\overset{|}{C}}}{-}\underset{\displaystyle SiEt_2H}{\overset{|}{N}}{-}R^2 \;=\; \mathbf{1}) \xrightarrow{MeOH} PhCHR^1NHR^2 \quad 85\text{-}96\%$$

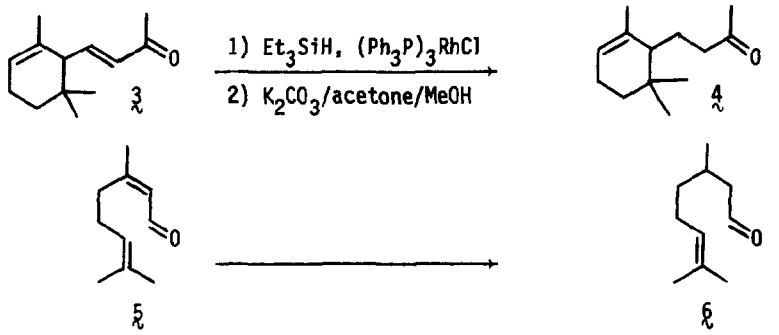
$$\mathbf{1} \xrightarrow{R^3COCl} PhCHR^1N(R^2)COR^3 \qquad (3)$$

R^1 = H, Me

R^2 = Me, Bu, Ph

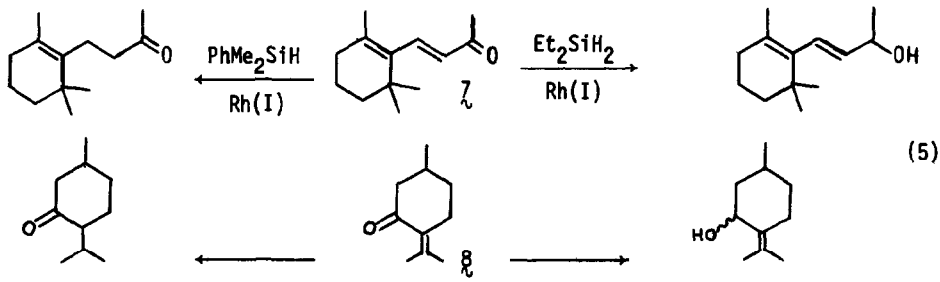
R^3 = Me, Ph

Silanes, in combination with rhodium(I) complexes, exhibit extraordinary selectivity for reduction of α,β-unsaturated carbonyls in the terpene series (6). α-Ionone 3 was converted to dihydroionone 4, and citral 5 to citronellal 6 by triethyl silane in the presence of 0.5 mole % of tris(triphenylphosphine)rhodium chloride, followed by dilute base hydrolysis of the intermediate silyl enol ethers. Glpc yields in excess of 95% and the complete absence of either double bond isomerization or carbonyl reduction were attractive features of these reactions (eq. 4).



(4)

With β-ionone 7 and pulegone 8, triethylsilane gave mixtures of ketonic and alcoholic products, whereas diethylsilane afforded mostly alcohol and phenyldimethylsilane mostly ketone (6) (eq. 5). The selectivity of these transformations exceeds that obtainable with either lithium aluminum- or sodium boro-hydride.



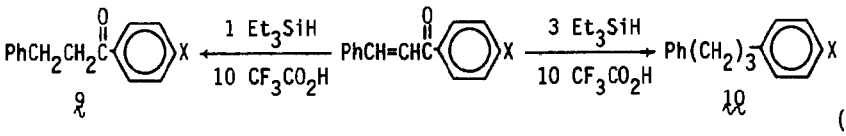
(5)

Arylcarbonyl compounds are smoothly reduced to aryl methylenes by excess triethylsilane in trifluoroacetic acid (14). Other alkylsilanes could be used without significant difference in yield. The best results were obtained using 2.2 equiv. of Et_3SiH and 5 to 10 equiv. of CF_3CO_2H at room temperature. The presumed intermediate secondary alcohols were not isolated except in cases where lactonization could intervene, e.g. o-benzoylbenzoic acid → 3-phenylphthalide. With cyclopropyl- and cyclobutyl-phenyl ketone ring expansion products were observed. Some typical examples with isolated yields are shown in eq. 6.

$PhCO(CH_2)_4COPh$	→ $Ph(CH_2)_6Ph$	72%
$(p\text{-}NO_2C_6H_4)_2C{=}O$	→ $(p\text{-}NO_2C_6H_4)_2CH_2$	96%
$PhCO(CH_2)_3CO_2H$	→ $Ph(CH_2)_4CO_2H$	59%
$CH_3OC_6H_4CH{=}O$	→ $CH_3OC_6H_4CH_3$	83%

(6)

Depending on the ratio of reagents, the triethylsilane/trifluoroacetic acid reduction of α,β-unsaturated aryl ketones can produce either saturated ketones or hydrocarbons (15). Ester, amide, carboxylic acid, nitrile, nitro, and sulfonic acid functions appear to be inert to this reagent for "ionic hydrogenation".

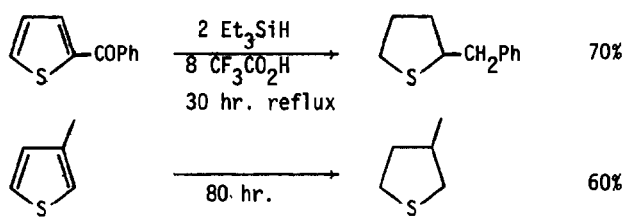


(7)

X =	H	F	Ph	CH_2CH_2Ph
Yield 9	80	75	79	77%
Yield 10	82	79	70	76%

The triethyl silane/trifluoroacetic acid combination was used for the simultaneous reduction of the 17-keto to a 17-OH and a Δ^8 or Δ^9 olefin function to a saturated linkage in a variety of estrone derivatives (16). One of the applications constituted a new estradiol synthesis (17).

Substituted thiophenes could be converted to the tetrahydro derivatives (thiophanes) by using a 1:2:8 ratio of substrate, triethylsilane, and trifluoroacetic acid. Yields of up to 80% were reported, and acyl groups on the ring were reduced concomitantly (18), fig. 8. The advantage of this non-catalytic procedure comes mainly from the avoidance of catalyst poisoning and desulfurization of the ring. As the time required for reduction was highly variable, i. e.



(8)

3-substituted compounds took longer, this reduction is a complex procedure mechanistically and worthy of further study. It has been noted that the polymeric Si-H function, $(MeSiH\text{-}O\text{-})_x$, is as effective as triethylsilane for "ionic hydrogenation (19), e. g. acetophenone → ethylbenzene (94%).

A mechanistic study of the synthetically attractive reduction of esters to

ethers with trichlorosilane and gamma rays, $RCO_2R' \rightarrow RCH_2OR'$, has been made and a sequence involving reductive hydrosilylation of C=O, Cl_2SiO extrusion, and α-chloroether hydrogenolysis proposed (20).

Partial reduction of α-trihalocarbonyls can be effected by the trimethylchlorosilane/HMPT/Mg system followed by dilute acid hydrolysis (21). Chloral afforded chloroacetaldehyde, while hexachloroacetone gave sym-tetrachloroacetone.

A variety of silane reductions of the P=O linkage are discussed in section VI of this survey.

III. CARBON-CARBON BOND FORMATION

A. Elimination Reactions

A report that olefins can be generated in modest yields by reaction of 2-bromoalkoxysilanes with magnesium in ether (22), e. g. $Me_3SiOCH_2CH(Ph)Br \rightarrow PhCH{=}CH_2$ (66%), should be followed up, particularly as the authors claim the synthesis of the yet unisolated trans-cyclohexene!! No experimental details were given.

Formation of benzyne by dehalosilylation of o-chlorophenyltrimethylsilane with inter alia $Et_4NF{\cdot}2H_2O$ or KOtBu (23), while intriguing from a mechanistic viewpoint, does not appear to offer synthetic advantages over the tried and true benzenediazonium carboxylate and aminobenzotriazole techniques.

Further studies on the reaction of steroidal olefins with the lead tetraacetate/trimethylsilyl azide combination have appeared (24-26) continuing the work of the Zbiral group which has been recently reviewed (27). The cholestadiene (24) and androstadiene (26) systems give mixtures of products and thus have limited synthetic utility, while Δ^5 monoolefins undergo the cleavage reaction (27) leading to ring-B-secosteroids in modest yield (25). The iodobenzene/trimethylsilyl azide reagent combination is more selective and general than $Pb(OAc)_4/Me_3SiN_3$ in its reactions with cyclic olefins (28). Use of 1:2:4 ratio of olefin:$PhI(OAc)_2$:Me_3SiN_3 in methylene chloride at -20^0 gave α-azidoketones in good yield from normal cyclic olefins. Strained olefins gave in addition the corresponding azidocycloalkane; this being the major product from benzo-

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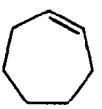
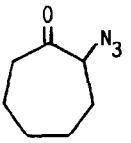
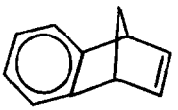
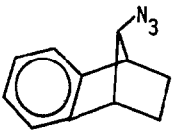
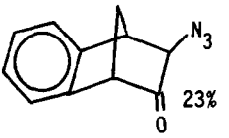
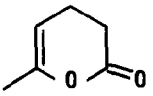
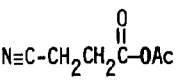
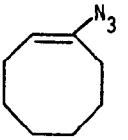
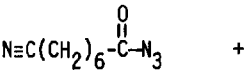
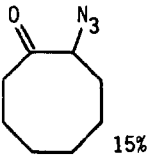
norbornadiene. These arise from direct reaction of olefin with azide and subsequent protodesilylation. With olefins bearing an unshared electron pair on an adjacent atom (enol ethers, vinyl halides) the following interesting specific cleavage occurs (eq. 9):

$$R'CH{=}CR''X \xrightarrow{PhI(OAc)_2/Me_3SiN_3} R'C{\equiv}N + O{=}C(R)X \qquad (9)$$

Although the mechanisms of these reactions remain hypothetical, the synthetic utility is demonstrated in Chart 1. Note the value of these transformations as an alternative to ozonolysis.

Chart 1

Conversions with the Olefin : 2 $PhI(OAc)_2$: 4 Me_3SiN_3 System

Olefin	Product(s) and Yield(s)
	 50%
	 65% +  23%
	 62%
	 40% +  15%

(10)

Deoxygenation of ketones to olefins by reaction with ethereal zinc and trimethylchlorosilane is the subject of a late communication (29). A mechanism involving an intermediate zinc carbenoid rather than a silyl enol ether was

favored because of the non-reactivity of the latter under the indicated conditions (eq. 11). The highly variable yields (cyclohexanone→ cyclohexene, 82% vs. cyclopentanone → cyclopentene, 14%) and intervention of pinacolization

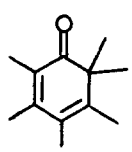
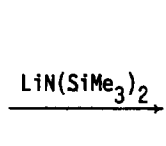
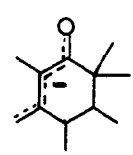
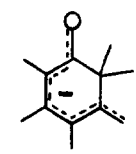
$$R\text{–}\overset{O}{\overset{\|}{C}}\text{–}CH_2R \xrightarrow[Et_2O,\ 18\ hr.]{5\ Me_3SiCl,\ 10\ Zn} RCH{=}CHR \qquad (11)$$

with acetophenone, together with the large excess of reagents required make this reaction at present far from general. Hopefully further study will clarify optimum conditions.

B. Alkylation of Carbon

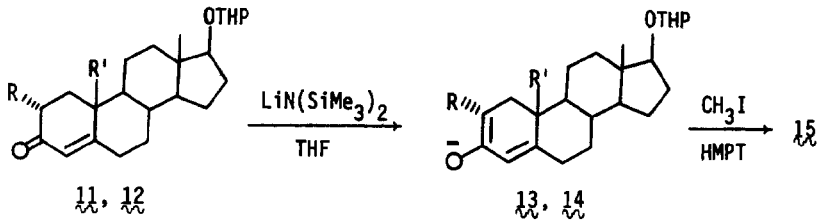
N-Lithio bis(trimethylsilyl)amide, $LiN(SiMe_3)_2$, has been the subject of several communications on the generation of enolates (30-33). Enolates of substituted malonates can be generated at low temperature (eq. 12)(30), and with dienones the γ- rather than the ε-proton is removed (eq. 13)(31).

$$(EtO_2C)_2CHR \xrightarrow[THF,\ -78^{o}]{LiN(SiMe_3)_2} (EtO_2C)_2CRLi \qquad R = H \text{ or } Me \qquad (12)$$

$$\xrightarrow{LiN(SiMe_3)_2} \quad \text{rather than} \qquad (13)$$

$LiN(SiMe_3)_2$ is a good base for conversion of the testosterone derivatives 11 and 12 to the thermodynamically less stable enolates 13 and 14. Alkylation of 13 leads to the 2-methyl-4-ene 15, rather than the 4,4-dialkyl-5-ene produced by KOtBu/MeI alkylation (32). Formerly, 15 was available only by a circuitous route.



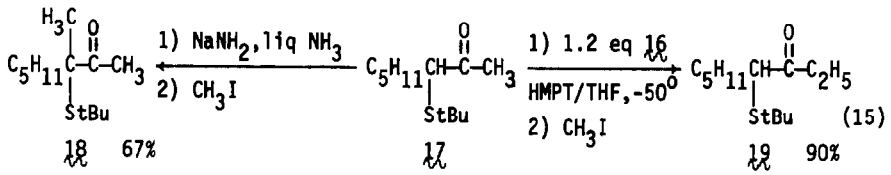
11, 12 13, 14 (14)

11, 13: R' = H, R = H

12, 14: R' = CH_3, R = H

15: R' = H, R = CH_3

Use of $LiN(SiMe_3)_2$ 16 as the base in the alkylation of α-t-butylthioketones directed alkylation to the methyl group, whereas sodamide afforded only alkylation at the more acidic position α to sulfur (eq. 15)(33). These results imply



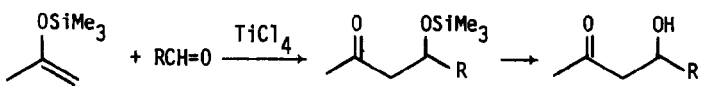
(15)

that kinetic control is the determining factor, and that the bulkiness of 16 is the determining factor. It is noteworthy that t-butylthioacetone is alkylated α to sulfur, even with 16, and that under regio-non-selective conditions, e. g. reaction at room temperature, 18 is produced rather than 19 when 16 is the base.

Cyclizations involving 16 as the base are discussed in section III-D.

Silyl enol ethers, R_3Si-O-C=C-, continue to be crucial in alkylation reactions at carbon, and a novel catalytic procedure for their preparation has been reported (34). Either a silylthiophenoxide and the ketone, or a silane, the ketone, and catalytic amounts of thiophenoxide and rhodium(I) are effective. For example, $PhCOCH_2CN + Et_3SiSPh \rightarrow PhC(OSiEt_3)=CHCN$ (90%) and $CH_3COCH_2COMe + Et_3SiH$ + 0.05 mole Et_3SiSPh + 0.01 mole $(Ph_3P)_3RhCl \rightarrow CH_3C(OSiEt_3)=CHCOMe$ (92%).

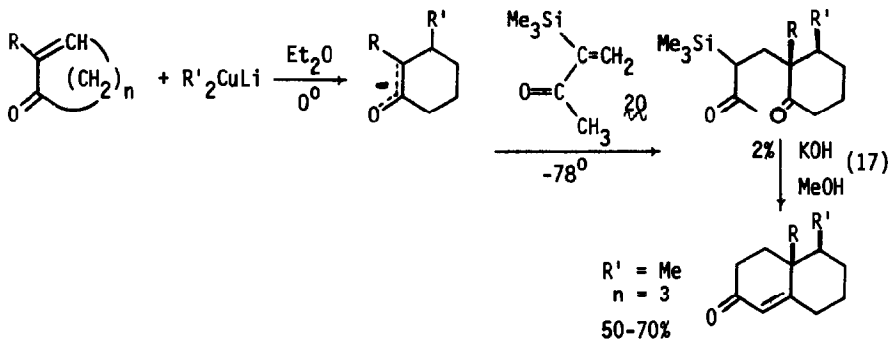
With $TiCl_4$ as catalyst, trimethylsilyl enol ethers are reported to undergo the aldol condensation with aldehydes and ketones (35) to give α-hydroxyketones.



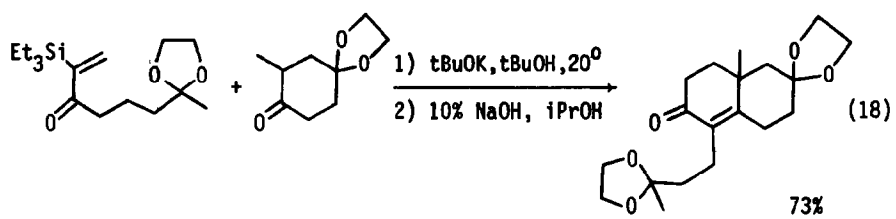
(16)

The use of lithium enolates derived from trimethylsilyl enol ethers in directed aldol condensations has been summarized by the House group (36).

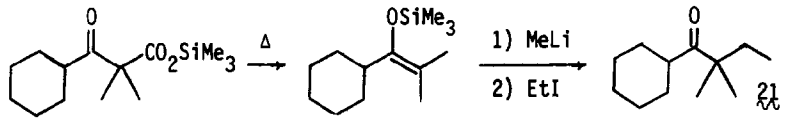
2-Trimethylsilylbut-1-ene-3-one 20 (37,38) is a useful synthon for the Robinson annelation of regio-unstable enolates, i.e. thermodynamically less stable enolates, which are generated by addition of lithium dimethyl cuprate to unsaturated ketones (38). Use of 20 rather than methylvinylketone leads to less polymerization (eq. 17). The α-silylvinyl ketones react readily with lithium



enolates (best generated from silyl enol ethers) at -78°. Lithium enolates react faster via proton transfer to generate the thermodynamically more stable enolate than they do with 20. A typical procedure, which failed completely with the non-silylated analog, is illustrated in eq. 18 (37).

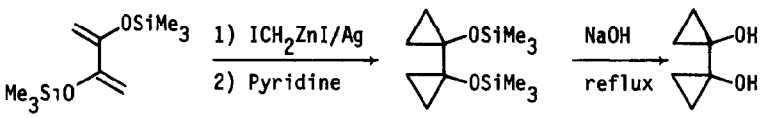


α-Quartenary ketones can be efficiently synthesized by alkylation of the silyl enol ethers produced by pyrolysis of trimethylsilyl-β-ketoesters. Thus t-amylcyclohexyl ketone 21 was prepared by the sequence in eq. 19 (39).



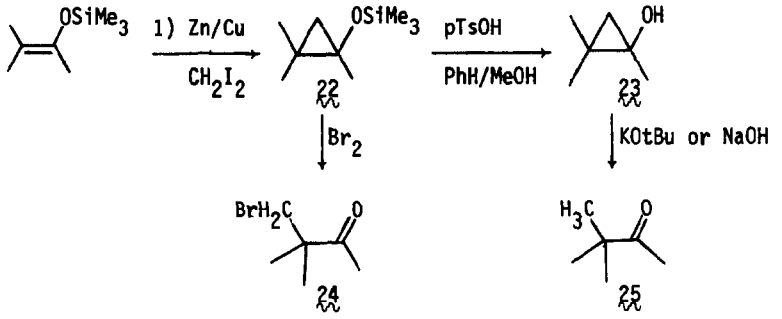
(19)

A number of groups have examined the consequences of adding the Simmons-Smith reagent to silyl enol ethers (40-44). Under the standard conditions of this reaction, siloxycyclopropanes 22 can be isolated by either pentane precipitation of the zinc salts (40) or successive washes of the ethereal solution with NH_4Cl, $NaHCO_3$, and H_2O (42). Bromination of 22 leads, in the bicyclo(n.1.0)alkane series, to α-bromomethyl ketones 24, e. g. cyclohexanone → 2-bromomethylcyclohexanone (42). For the isolation of the exquisitely acid sensitive cyclopropanols 23, desilylation can be carried out with either toluenesulfonic acid in methanol/benzene or by refluxing in methanol (41). If no significant precautions are taken the reaction leads to mixtures of 22 and 23 (43). Alternatively, as in the synthesis of cyclopropanone pinacol 27, a zinc/silver couple may be used, and excess ZnI_2 precipitated with pyridine (41). It is interesting to note that the bis-silyl enol ether 26 was obtained not from biacetyl but rather by thermolysis (180°) of the silylacyloin product of diethyl succinate (see section III-D). The synthetic utility of siloxycyclopropanes is illustrated by their use in the synthesis of α-methylketones 25 (43,44). Cleavage of 23 with potassium t-butoxide gives yields in the 70-80% range (43), e.g. acetophenone → propiophenone. If methanolic sodium hydroxide is employed as the cleaving reagent, yields are lower, but the reaction can be used for the specific α-methylation of aldehydes (heptanal → 2-methylheptanal) α,β-unsaturated ketones (testosterone → 4-methyltestosterone, via a silyl dienol ether), or utilizing regio-specific silyl enol ethers, conversion of 2-methylcyclohexanone to either the 2,2- or 2,6-dimethyl derivative could be realized (44). These reactions are summarized in eq. 20 and 21.



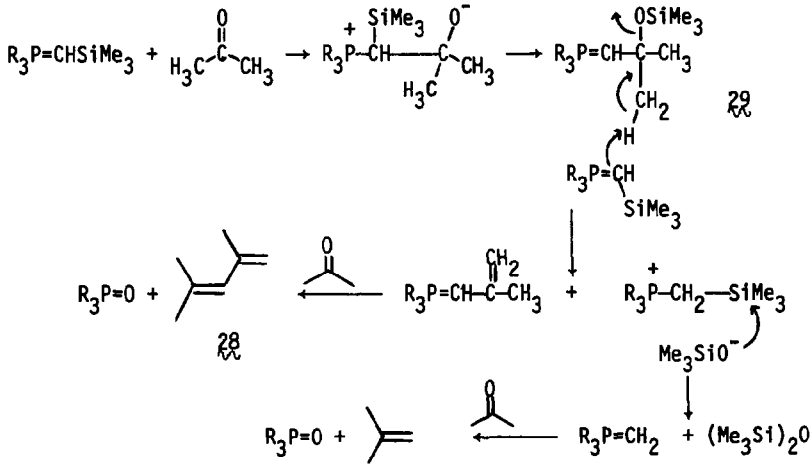
26 27

(20)



(21)

An unusual olefin synthesis involving silylated ylides has been reported by the Schmidbaur group (45). The stoichiometry 3 $R_2C{=}O$ + 2 $R'_3P{=}CHSiMe_3$ ⟶ $R_2C{=}CH_2$ + $R_2C{=}C{=}CR_2$ + 2 $R'_3P{=}O$ + $(Me_3Si)_2O$ is necessary, as are pure salt-free (i.e. distilled) ylides. The yield in the R = R' = Ph case was quantitative, while R = R' = CH_3 gave the butadiene 28 rather than tetramethylallene. The mechanism proposed (eq. 22) involves desilylation of siloxy ylide 29. In the

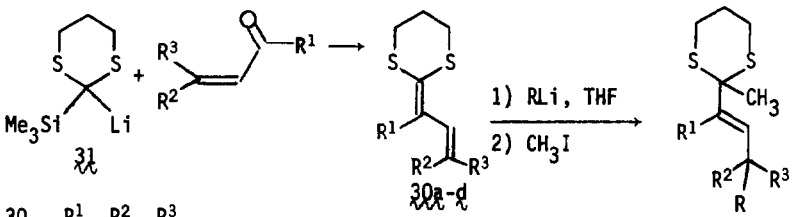


(22)

R' = Me, R = Ph case, prototropic rearrangement of an intermediate ylide gave $Ph_2C{=}CH{-}P(O)Me_2$ and two moles of $Ph_2C{=}CH_2$ rather than tetraphenyl allene.

The silicon equivalents of Wittig reagents, $R_2Si{=}CH_2$, can be generated by pyrolysis of silacyclobutanes (46). They react with aldehydes, but not ketones, to generate olefins, e. g. heptanal ⟶ 1-octene (35%). Synthetically, however, this reaction will be useful only on planets without phosphorus.

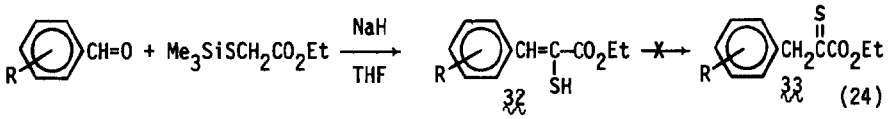
Conjugated ketenethioacetals 30, prepared by reaction of 2-lithio-2-trimethylsilyl-1,3-dithiane 31 with α,β-unsaturated carbonyl compounds, undergo Michael reaction with alkyl lithiums to yield dithiane anions (eq. 23) which upon alkylation or protolysis, afford products corresponding to a conjugate addition in the reverse sense, i.e. C=C–C=O → Electrophile–C=C–C–Nucleophile (47).



(23)

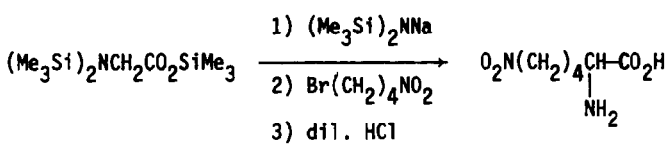
30	R^1	R^2	R^3
a	H	H	H
b	H	H	CH_3
c	CH_3	H	H
d	$-(CH_2)_3-$		H

Fragrant α-mercaptocinnamate esters 32 are prepared in 48-80% yield by the condensation of ethyl (trimethylsilylthio)acetate with substituted benzaldehydes (eq. 24). The tautomeric thioketo form 33 was not observed in the pmr spectrum, nor was the reaction attempted with aliphatic aldehydes (48).



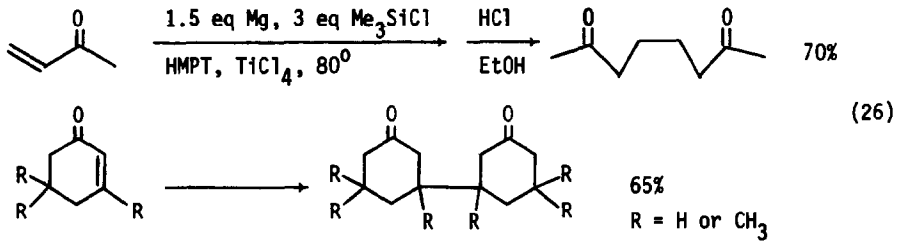
(24)

The Ruhlmann aminoacid synthesis has been employed to prepare 6-nitro-2-aminohexanoic acid, a blocked lysine for peptide synthesis (49)(eq. 25). The nitro function inhibits condensations at the ε-position, which is a constant problem with lysine in peptide synthesis, leading to incorrect sequences.



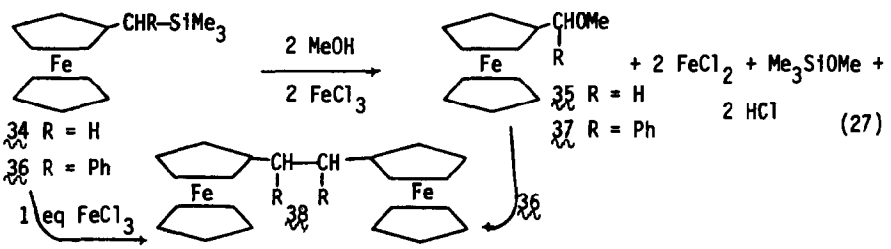
(25)

Dimerization of α,β-unsaturated ketones at the 4,4'-position is possible with the Me_3SiCl/Mg/HMPT provided that the C=C–C=O sequence is not conjugated with an Ar-, -C=C-, or -N- group (50). The results (eq. 26) are quite sensitive to reaction conditions, with pinacolization (1,1'-coupling) and 1,4-disilylation intervening in certain conditions. The synthetic usefulness of this 1,6-diketone preparation appears promising, and is worthy of intensive further study. A mechanism involving $Me_3Si\cdot$ is implicated by the experimental data.



(26)

Derivatives of silylmethylferrocenes readily solvolyse in alcoholic ferric chloride solution, e. g. 34 – 35 (eq. 27). In the R = aryl series, if only one equivalent of ferric chloride is used, the major product is the diaryldiferrocenyl ethane 38 (51). Mixed coupling products can be obtained. A mechanism involving benzylferrocenyl radicals, $Fc\dot{C}HAr$, which are generated from both 36 and 37, was implicated (51, 52).



(27)

Oxidative coupling of hindered trimethylsiloxyphenols with benzoyl peroxide has been studied, and shown to produce some interesting dimeric products (53). Some studies on the silylation of malonic acid have been reported (54). With the utility of malonic esters in organic synthesis, this area appears to be a rich field to harvest.

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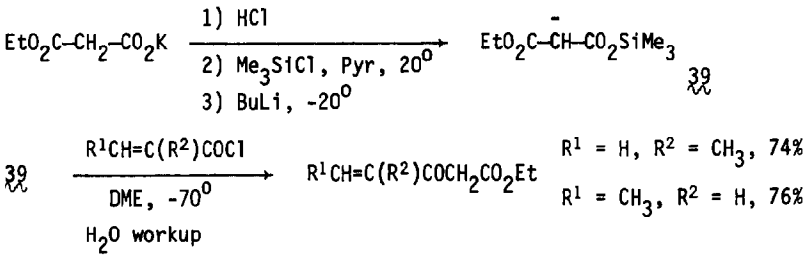
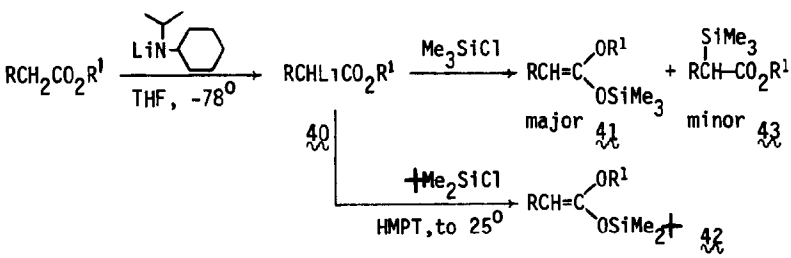
C. Acylation of Carbon

A superior synthesis of a key synthon for Robinson annelation and piperidone synthesis: ethyl acryloylacetate and its homologs, has been communicated (55). Acylation of silyl ethoxycarbonylacetate 39 gives the yields shown in eq. 28. The major advantage of this variant of the malonic acid synthesis is that the hydrolysis and decarboxylation of the intermediate diacid can be carried out under strictly neutral conditions.

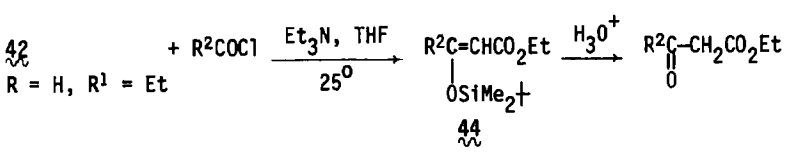


(28)

The preparation of O-silyl keteneacetals, e. g. 41 and 42, has been simplified. These are valued synthetic equivalents of ester enolates. Trimethylchlorosilane reacts with lithio esters 40, generated via lithio isopropylcyclohexylamide, to give predominant O-silylation as shown in eq. 29 (56). Use of t-butyl esters (R^1 = tBu), acetates (R = H), or addition of HMPT to the reaction mixture led to increased formation of the synthetically less useful C-silyl esters 43. The more stable O-t-butyldimethylsilyl keteneacetal 42 was



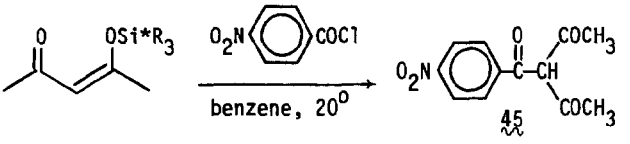
(29)



R^2 = Me, nPr, iPr, Ph, tBu, t-C_6H_{11}, MeCH=CH-; 40-98%

prepared with HMPT cosolvent, but was not accompanied by any C-silylation. This reagent is especially useful in the synthesis of β-ketoesters. When 42 was condensed with acid chlorides in the presence of triethyl amine (eq. 29) silyl enol ethers of keto esters 44 can be isolated and characterized. Hydrolysis affords β-keto esters. These compounds have intriguing, as yet unexplored synthetic possibilities (57).

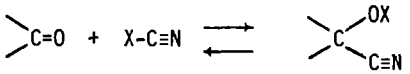
The related silyl enol ethers of β-dicarbonyl compounds, which can be made in optically active form (58), e. g. (–)$EtO_2CCH{=}C(OSi^*R_3)OEt$, Si^*R_3 = MePhNpSi, react with acid chlorides to afford triacylmethanes, e. g. 45, as shown in eq. 30.



45 (30)

The possibility of using these reagents for asymmetric synthesis should definitely be explored (59).

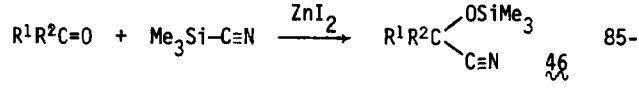
Several groups (60-66) have investigated the use of trimethylsilyl cyanide as a reagent for introducing -C≡N functionality, acylation, protecting, and activating carbonyl groups. The cyanohydrin equilibrium, eq. 31, is strongly shifted



(31)

to the right on replacing X = H with X = Si ($\Delta H_{Si} - \Delta H_H \approx$ 20 kcal/mol) (60).

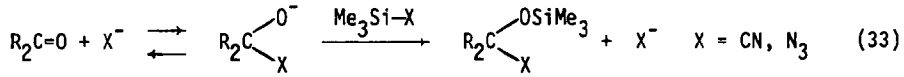
Thus, use of trimethylsilyl cyanide for direct cyanosilylation affords cyanohydrin derivatives not accessible from the parent carbonyls. Aldehydes, ketones (which are generally unreactive with HCN), and α,β-unsaturated carbonyls all reacted smoothly when heated without solvent with Me_3SiCN in the presence of 1/300 equivalent of zinc iodide (eq. 32)(60). Quinones (62), dialdehydes (66),



(32)

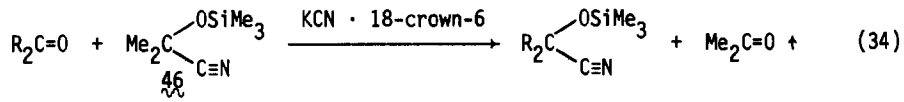
and acetylacetone react analogously, although the latter affords the monosilyl enol ether $MeCOCH{=}C(OSiMe_3)Me$ unless a large excess of Me_3SiCN is employed (66).

In lieu of Lewis acid catalysts, anionic reagents are equally effective in cyanosilylation (61). For example, KCN-crown ether complex in 0.02 molar equivalent catalysed the cyanosilylation of 3-pentanone, 4-t-butylcyclohexanone, and benzoquinone in 80-99% yield. Azidosilylation, but not thiocyanatosilylation was similarly catalysed. Mechanistically, the process of eq. 33 seems plausible.



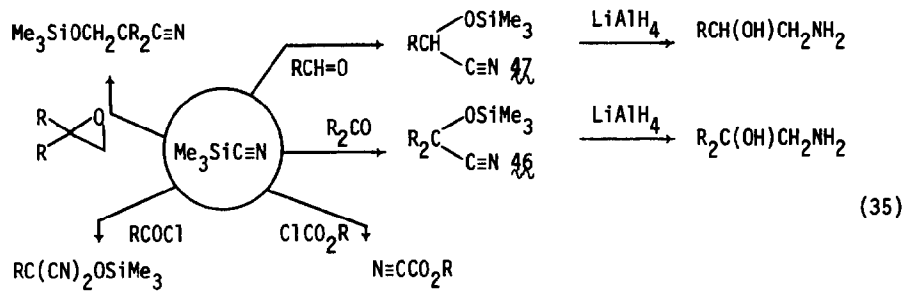
$$R_2C{=}O + X^- \rightleftharpoons R_2C(O^-)X \xrightarrow{Me_3Si{-}X} R_2C(OSiMe_3)X + X^- \quad X = CN, N_3 \qquad (33)$$

Silylation of commercially available acetone cyanohydrin to 46 ($R^1 = R^2 = Me$) obviates the need for the expensive trimethylsilyl cyanide reagent, as 46 undergoes catalytic trans-cyanosilylation readily via a process machanistically related to the Meerwein-Pondorf-Verley reduction (eq. 34)(61).



$$R_2C{=}O + Me_2C(OSiMe_3)(C{\equiv}N) \quad (46) \xrightarrow{KCN \cdot 18\text{-crown-6}} R_2C(OSiMe_3)(C{\equiv}N) + Me_2C{=}O \uparrow \qquad (34)$$

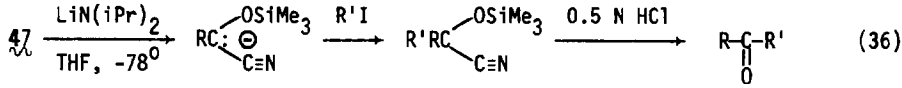
The synthetic versatility of trimethylsilyl cyanide as a cyano-transfer reagent is great. Besides the aforementioned conversion of aldehydes and ketones to cyanohydrins (60,63), epoxides afford β-siloxynitriles (64), acid chlorides give siloxymalononitriles (63, 64), and chloroformates cyanoformates (64). These reactions, together with the reduction of 46 to β-aminoalcohols (60) are detailed in eq. 35.



$Me_3SiOCH_2CR_2C{\equiv}N$; $Me_3SiC{\equiv}N$; RCH=O → $RCH(OSiMe_3)(C{\equiv}N)$ 47 ; R_2CO → $R_2C(OSiMe_3)(C{\equiv}N)$ 46 ; RCOCl → $RC(CN)_2OSiMe_3$; $ClCO_2R$ → $N{\equiv}CCO_2R$; $LiAlH_4$ → $RCH(OH)CH_2NH_2$; $LiAlH_4$ → $R_2C(OH)CH_2NH_2$ (35)

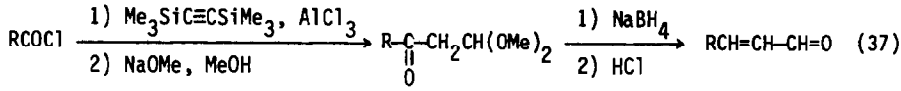
A formal acylation of carbon, the conversion of an aldehyde to a ketone, is achieved by treatment of the anion of a siloxy-aldocyanohydrin, i. e. 47, with an alkyl halide. The ketone is produced by mild acid hydrolysis, eq. 36 (65).

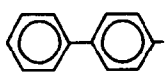
This method, formally equivalent to the Corey-Seebach 1,3-dithiane alkylation, offers significant advantages in convenience and versatility, particularly in the case of furfural, where the dithiane synthesis fails. Aliphatic aldehydes are ill-suited for the present sequence, however.



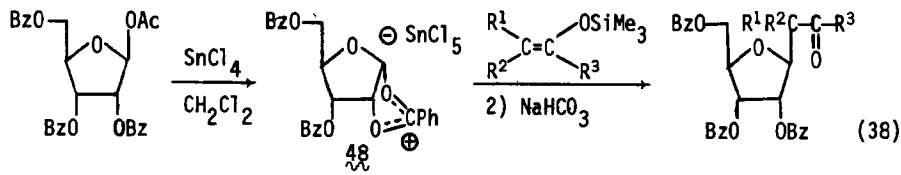
R = Aryl, R' = Me, $PhCH_2$, Et, iPr, etc. 59-98% (36)

Treatment of an acid chloride with bis(trimethylsilyl)acetylene affords a silylethynyl ketone, as is well known from the work of the Walton group. When this ketone is successively treated with methanolic methoxide, sodium borohydride, and 4 N hydrochloric acid in aqueous dioxane, α,β-unsaturated aldehydes are obtained in excellent yield (67)(eq. 37)



R = Ph (78%),  (45%),  (84%) (37)

In a variation of a well-known technique for nucleoside synthesis, C-ribosides are prepared by combination of silyl enol ethers with acyloxonium ions, i.e. 48. This produces compounds (eq. 38) in 34-95% yield which can be elaborated to biologically important C-nucleosides, e. g. pseudo-uracil (68).



48

(38)

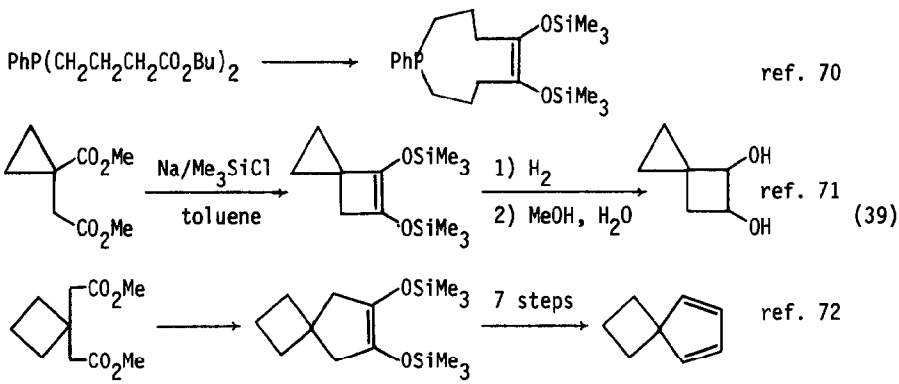
R^1 = H, $R^2 + R^3 = (CH_2)_4$, 95%

R^1 = H, $R^2 = CO_2Bz$, R^3 = OBz , 43%

$R^1 = CH_2CO_2Et$, $R^2 = CO_2Et$, R^3 = OEt , 50%

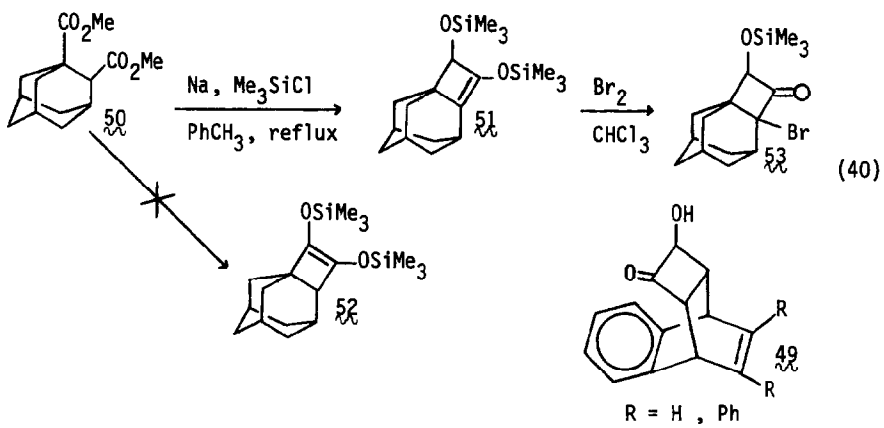
D. Cyclization and Ring-Forming Reactions

The Rühlmann Modification of the acyloin reaction, reviewed in 1971 (69), which produces bis(silyloxy)enediols when diesters are treated with sodium and trimethylchlorosilane in an aromatic solvent, continues to find widespread application in the construction of four- to nine-membered rings. Some examples (70-73) are shown in eq. 39.



(39)

Use of the silyl-acyloin synthesis to prepare strained polycycles has continued apace (73,74). The novel tetracyclic acyloin 49 was obtained by methanolysis of the intermediate bis(silyloxy) enediol obtained from the corresponding diester (73). Treatment of dimethyl adamantane-1,2-dicarboxylate 50 under the conditions of the silyl-acyloin synthesis afforded, rather than the expected 52, the double-

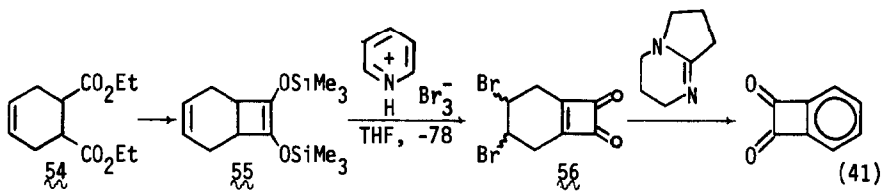


(40)

bond isomer 51. The normal acyloin was obtained upon treatment of 51 with methanol, however bromine in chloroform gave the interesting bromoketone 53, eq. 40. Lack of formation of 52 was attributed to the rigidity of the adamantane skeleton prohibiting simultaneous sp^2 hybridization at the carbons bearing siloxy groups (74), although it appears that 51 is no less strained than 52.

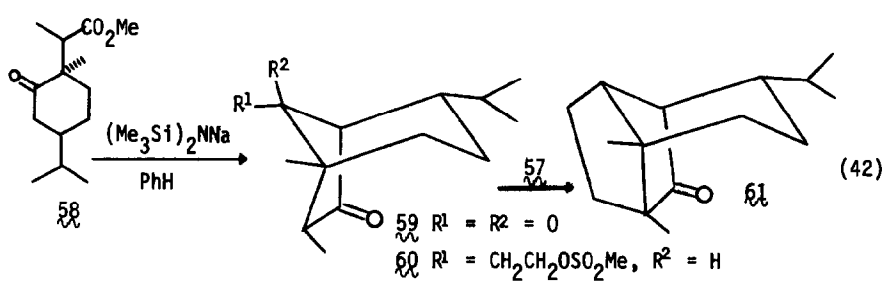
A novel transformation of the bis(silyloxy) enediol derived from diethyl 4-cyclohexene-1,2-dicarboxylate, leading to the elusive benzocyclobutadiene quinone, has been described by Kowar and Le Goff (75). Cyclization of 54 to 55 was followed by oxidation with pyridinium tribromide, leading (via an intermediate tribromide) to quinone 56, which was dehydrobrominated with DBN in good yield to the desired quinone (eq. 41).

The combination of steric bulk, high basicity, and low nucleophilicity of lithio bis(trimethylsilyl)amide have been alluded to in section III.B (33).



54 55 56 (41)

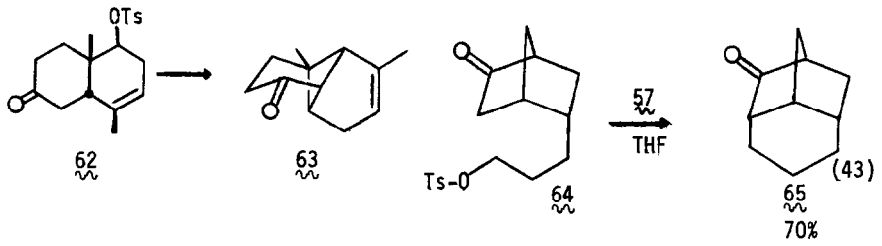
It is thus natural that this base be used in cyclizations where enolate ions are to be generated at specific locations. Thus in a multi-step sesquiterpenoid synthesis, $NaN(SiMe_3)_2$ 57 was employed three times (76). Intramolecular Claisen condensation of 58 to 59 failed with NaH, Ph_3CLi, and Ph_3CNa, but proceeded in 76% yield when a 2.6-fold excess of 57 was employed. Later, intramolecular alkylation of mesylate 60 with the same reagent in dimethoxyethane afforded ylangocamphor 61 in 84% yield (eq. 42).



58 59 R1 = R2 = O 61 (42)

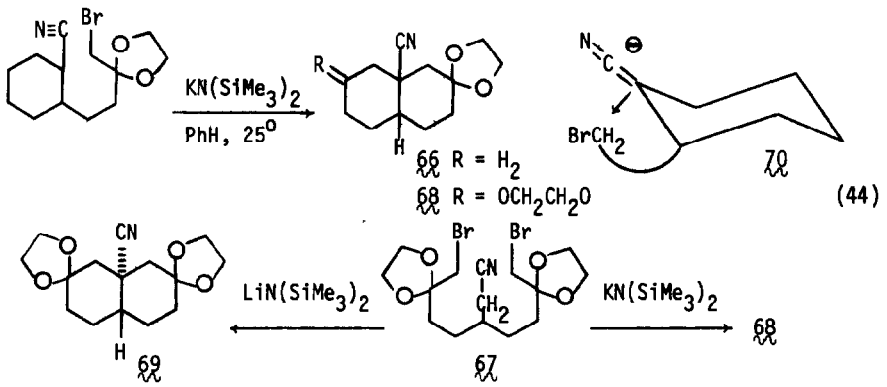
60 R1 = $CH_2CH_2OSO_2Me$, R2 = H

Sodio bis(trimethylsilyl)amide effected the cyclization of 62 to 63, part of a ylangene synthesis, in low yield, but was not as effective as sodium methylsulfinyl methylide (77)(eq. 43) while the base of choice for conversion of ketotosylate 64 to 2-homobrendanone 65 was sodio bis(trimethylsilyl)amide in THF (78).

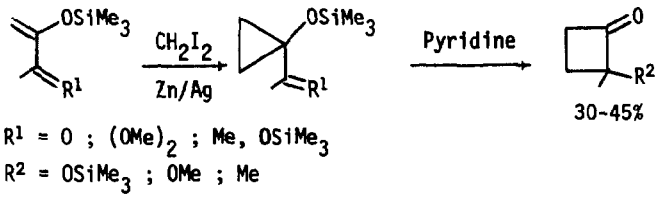


62 63 64 65

Potassio bis(trimethylsilyl)amide is effective for the cyclization of ketals of ε- and ζ-bromonitriles to cyanocyclo-pentanes and -hexanes (79). The examples of eq. 44 demonstrate that cis-fusion predominates in the decalin series, and that two rings can be formed at once, e. g. 67 → 68. Use of lithio bis(trimethylsilyl) amide, however, leads to the thermodynamically more stable trans-decalin 69 (80). The stereochemical control is considered to result from attack of an initially generated potassio carbanion on an axially held chain, i. e. 70.



Cyclopropyl silyl ethers in which a β-carbon possesses a partial positive charge, i.e. 1-trimethylsiloxy-1-(X)-cyclopropane, (X) = C-Hal, C-OTs, C-OSiMe$_3$, C=O, C=C, readily accessible from the corresponding ketones (see section III.B) are converted by mild treatment, e. g. pyridine in the examples of eq. 45, to cyclobutanones, thus constituting a new synthetic entree to this difficultly preparable series (81).

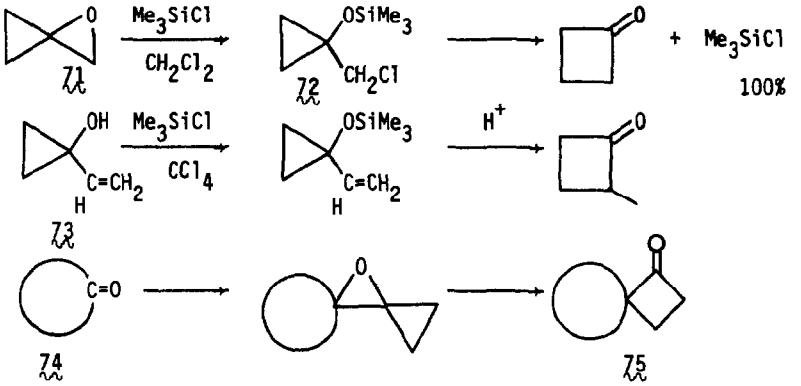


(45)

R^1 = O ; $(OMe)_2$; Me, $OSiMe_3$

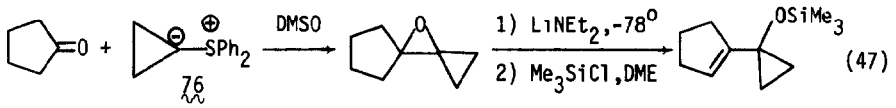
R^2 = $OSiMe_3$; OMe ; Me

Oxaspiropentane 71 is quantitatively converted to cyclobutanone itself by treatment with trimethylchlorosilane at room temperature (presumably via silylchlorohydrin 72) while vinyl cyclopropanol 73 gives 2-methylcyclobutanone under similar conditions (eq. 46)(81,83). Rearrangement of an oxaspiropentane is a key feature of a novel cyclobutanone spiroannelation (74 → 75) reported by the Trost group (82,83). Treatment of a ketone successively with diphenylsulfonium

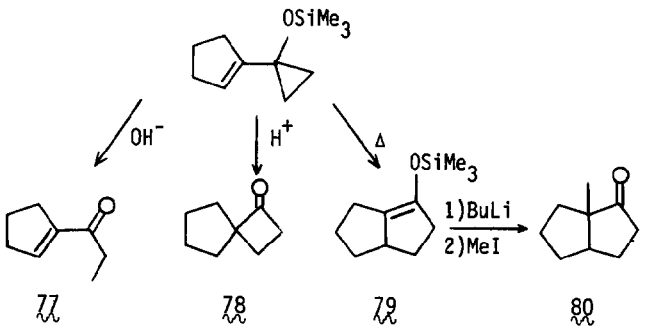


(46)

cyclopropylide 76 in DMSO, lithio diethylamide, trimethylchlorosilane and dimethoxyethane affords a 1-vinyl-1-trimethylsiloxycyclopropane in 80-95% yield, as illustrated for cyclopentanone in eq. 47. Base treatment of this versatile synthon gives a alkyl vinyl ketone 77, acid treatment ring expansion to the cyclobutanone 78, while thermolysis gives a silyl enol ether 79 via the vinylcyclopropane rearrangement. As 79 can be alkylated at the bridgehead position to 80, the use of this reaction sequence for construction of the D-ring of steroids in the androsterone series seems a logical extension. Uniformly high yields, and applicability to a wide variety of alicyclic ketones were attractive features of this sequence (82).

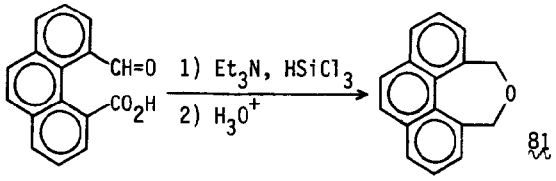


(47)



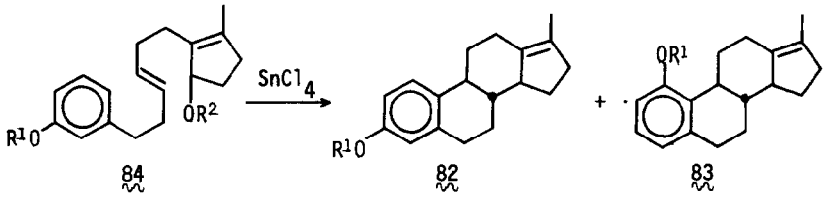
(48)

When applied to 5-formyl-4-phenanthroic acid or phenanthrene-4,5-dicarboxylic acid, reductive silylation by the Benkeser procedure unexpectedly gave the cyclic ether 81 rather than 4,5-dimethylphenanthrene (eq. 49). No mechanism for this transformation was offered (84).



(49)

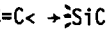
In the biogenetically patterned cyclization of 84 to 82, a key step in a new oestrone synthesis (85), the use of $R^1 = Me_3Si$ gave a 82:83 ratio of 8.4:1 compared to 1.4:1 for the R^1 = Me, R^2 = H compound, when cyclization was carried out with stannic chloride (3 equivalents) in methylene chloride at -75° (86). This ratio could be increased to 20:1, and the yield made nearly quantitative, by utilizing inverse addition at -100° (85). As the disilyl derivative $R^1 = R^2$ =



(50)

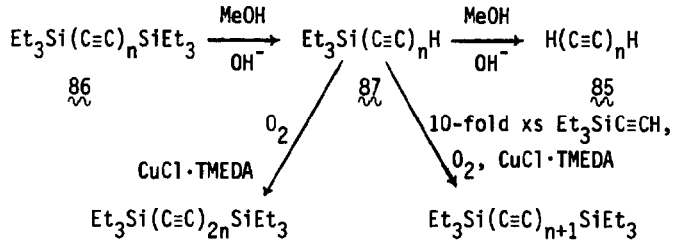
Me_3Si has an 82:83 ratio of but 2.6:1, selective silylation of the phenolic hydroxyl was necessary, and was accomplished by use of $CF_3C(OSiMe_3)=N\text{-}SiMe_3$ at 0^o .

The use of α-silyl-α,β-unsaturated ketones as synthons in the Robinson Annelation has been discussed in section III.D (37,38), as has the cyclopropanation of silyl enol ethers (40-43).

Some years ago, the work of Haszeldine added the trichloromethylsilyl group to the family of dihalomethylene transfer agents by showing that these reagents can dichlorocyclopropanate olefins ($Cl_3CSi\langle + >C=C< \rightarrow \rangle SiCl +$ ) upon thermolysis. However, the synthetic utility of these reagents has suffered from their relative inaccessibility, Lewis acidity, and atmospheric sensitivity. However, the availability of a spectrum of $YSiCCl_3$ compounds with differing decomposition temperatures (87): Y = F_3, 100^o; Y = Cl_3, 210^o; Y = $(CCl_3)Cl_2$, 220^o; Y = $(OEt)_3$, 238^o, gives flexibility to the reaction. The eximious CX_2-transfer reagents remain the trihalomethylmercurials.

E. Acetylene Synthesis

The use of an R_3Si- as a protecting or activating function for the acetylenic C–H continues to be a vigorously prosecuted technique, with the Walton group making important contributions. Their work in the polyacetylene series has been described in full (88). Compounds of the polyyne series 85 ($n \leq 12$) and 86 ($n \leq 16$) have been prepared with the aid of the Et_3Si- group as a masking function (88). Ethyne 87 (n = 1) and butadiyne 87 (n = 2) are prepared in straightforward fashion from the acetylene Grignard reagents and Et_3SiBr. These are oxidatively coupled in acetone solution with a CuCl·TMEDA catalyst. Cleavage of a single Et_3Si- group from polyyne 86 is accomplished by addition of methanolic base; advantage being taken of the fact that, with equal n, cleavage of 86 is twice as fast a cleavage of 87. Monosilylpolyyne 87 can either be coupled with itself or, to prepare n-odd members of the series, with a tenfold excess of $Et_3SiC{\equiv}CH$ (to facilitate separation from the symmetrically coupled products).



(51)

Complete desilylation (basic conditions) affords the unstable parent polyynes 85, which were handled exclusively in hydrocarbon solution. Eq. 51 summarizes these transformations. These reactions were monitored by ultraviolet spectroscopy, taking advantage of the intense, regularly spaced, electronic spectra of polyynes, which obey the $\lambda^2 = kn$ (n = number of C≡C units) rule.

The Et_3Si- masking group was favored since it could be removed under milder conditions than other commonly used protecting groups in acetylene synthesis, e. g. CO_2H or CO_2Et, and yet could survive the oxidative coupling as well. Trimethylsilyl groups on $Me_3Si(C{\equiv}C)_nSiMe_3$, n > 4, are not effective masking functions as they suffer cleavage in 'neutral' methanol (88).

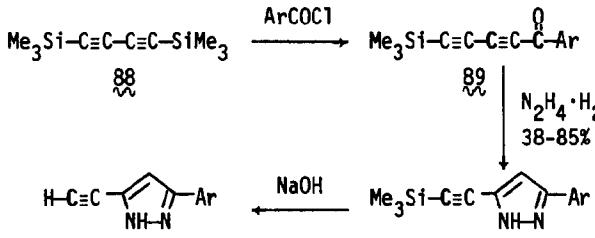
A general synthesis of aryl acetylenes from aryl halides has been communicated (89). Condensation of iodoethynyltrimethylsilane and the appropriate aryl copper, followed by mild alkaline hydrolysis affords aryl acetylenes in good yield (eq. 52).

$$Me_3SiC{\equiv}CSiMe_3 \xrightarrow{ICl} IC{\equiv}CSiMe_3 \xrightarrow{Ar\text{-}Cu} ArC{\equiv}CSiMe_3 \xrightarrow{OH^-} ArC{\equiv}CH \qquad (52)$$

Ar = Ph, subst. Ph, napthyl, furyl, thienyl, etc. 30-80% overall

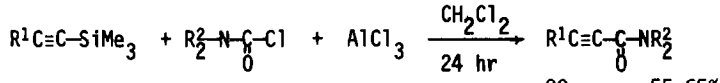
The synthesis of 3-aryl-5-ethynylpyrazoles is accomplished by a fusion of the classical preparation of pyrazoles by addition of hydrazine to an acetylenic ketone with this contemporary polyacetylene technology (90). Diyne 88 gives butadiynyl ketone 89 upon coupling with acyl halides (91). Treatment with hydrazine hydrate and subsequent base hydrolysis gives the ethynyl pyrazole (eq. 53).

Similarly, carbamoyl chlorides react with silyl acetylenes in the presence



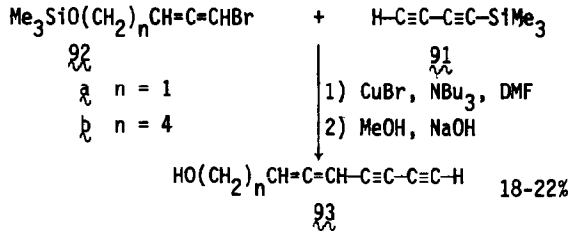
Ar = C_6H_5-, p-$NO_2C_6H_4$, p-ClC_6H_4, furyl, ½ -pC_6H_4-

of aluminum chloride to afford acetylenic amides, i. e. 90, in good yield (92).

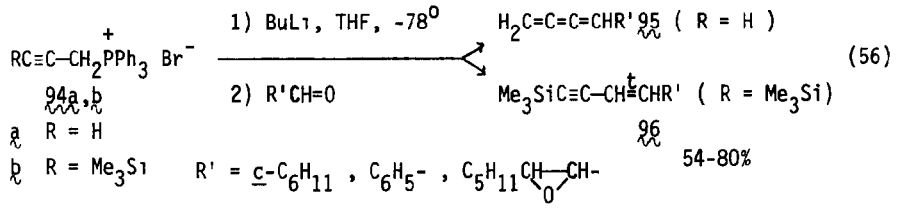


R^1 = nC_4H_9, nC_5H_{11} ; R^2 = -$(CH_2)_4$-, -$(CH_2)_5$-, -Et

Synthesis of two naturally occuring acetylenic allenes has been reported by Ugandan workers (93). Silyl-blocked diyne 91 (91) was coupled with siloxy bromoallene 92, yielding 93 after desilylation of both protected functions (eq. 55). The low yields could possibly be improved by using borax/methanol cleavage to remove acetylenic silyl groups (88).

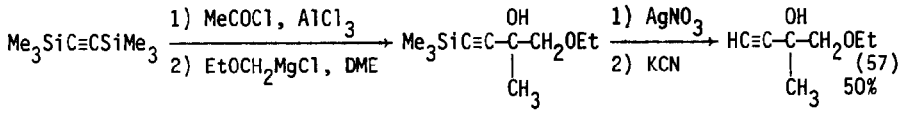


The stereoselective synthesis of terminal enyne units has been outlined by Corey and Ruden (94). An attempted Wittig reaction of propargyltriphenylphosphonium bromide 94a with aliphatic aldehydes gave a cumulene 95 rather than the desired enyne 96, which compound was obtained in good yield by a Wittig reaction on silyl-protected phosphonium salt 94b (eq. 56). Predominant <u>trans</u>-stereochemistry was observed. The <u>cis</u> enyne, the form usually found in natural products, was prepared by a different route, and isolated as the trimethylsilyl-protected



derivative. Protecting groups were quantitatively removed by treatment with tetrabutylammonium fluoride.

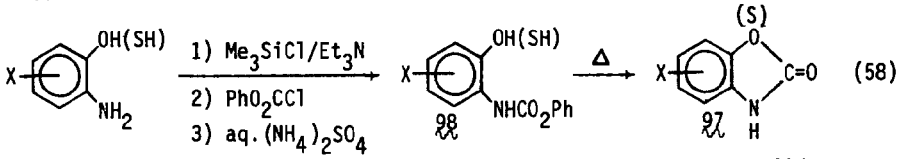
The sequence in eq. 57 nicely illustrates the protective function of silyl groups in the synthesis of a polyfunctional acetylene (95). Additional examples of silyl protecting functions are found in section VII.



IV. FORMATION OF BONDS TO HETEROATOMS

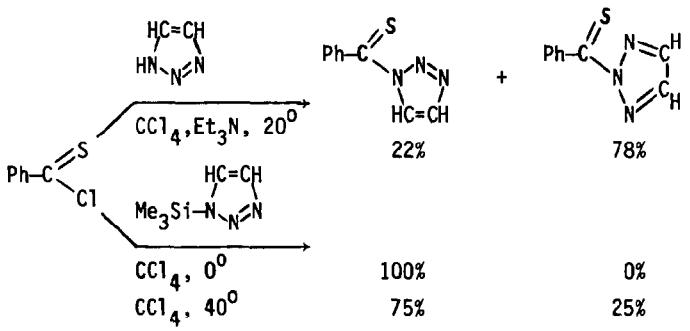
A. Acylation and Alkylation of Nitrogen

A now standard amide synthesis involves reaction of a silyl amine with an acid chloride (1). Several examples reported this year offer novel extensions of this technique. For example, a convenient synthesis of oxa- and thia-zolidone derivatives 97 involves silylation of an o-aminophenol or thiophenol, followed by phenyl chloroformate treatment, to afford after hydrolysis the carbamates 98 which are readily cyclized in boiling toluene or chlorobenzene to the heterocycles 97 (96)(eq. 58).



Acylation of the silylamines produced by hydrosilylation of Schiff bases

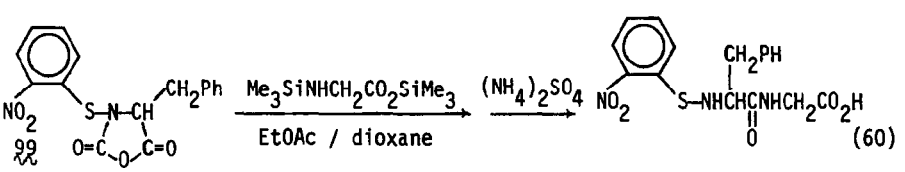
(13) has been previously discussed (eq. 3). High molecular weight aryl phthalimides are produced by refluxing N,N-disilylaniline derivatives with phthalic anhydride (97), illustrating the analogous reaction of silylamines with anhydrides. Similarly, thioacylation of silylamines is possible, and in the case of trimethylsilyltriazole, gives products different from those obtained with the parent base (98). As illustrated in eq. 59, the 1-thiobenzoyl derivative is the major product with silyl triazole, while triazole gives mostly the 2-derivative.



(59)

Thiobenzoyltriazoles are powerful thioacylating agents. However, thiobenzoyltetrazole, prepared from trimethylsilyltetrazole and thiobenzoyl chloride, exploded at 50° (98).

The utility of silylamines in peptide synthesis continues to be exploited, although applications in this field have yet to become general. As an illustration, the reaction of disilyl glycine with the N-sulfenylamino-N-carboxyanhydride of phenylalanine 99, affords N-sulfenyl-Phe-Gly after stripping the silyl functions from the dipeptide with ammonium sulfate (99). This N-carboxyanhydride process (eq. 60) is useful because racemization is avoided.



(60)

The sequence of eq. 61 illustrates how trimethylsilyl groups both activate and protect serine and threonine in peptide synthesis by the N-carboxyanhydride method. The O-silyl function disappears in the coupling step (100).

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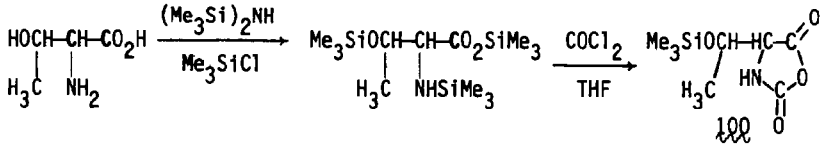
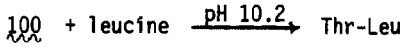
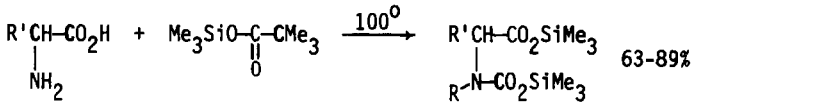


(61)



In lieu of the traditional trimethylsilyl protecting function for peptide synthesis, Tarbell and coworkers explored the advantages of the trimethylsiloxycarbonyl function (101) by preparing a series of derivatives of various amino acids with t-butyltrimethylsilyl carbonate (eq. 62). It is interesting to note that only valine, among the amino acids surveyed, retained an N-H, while all

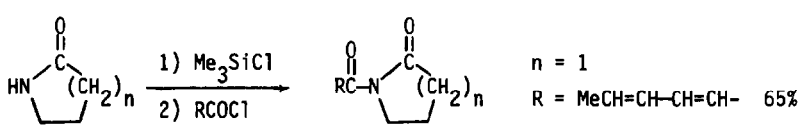


(62)

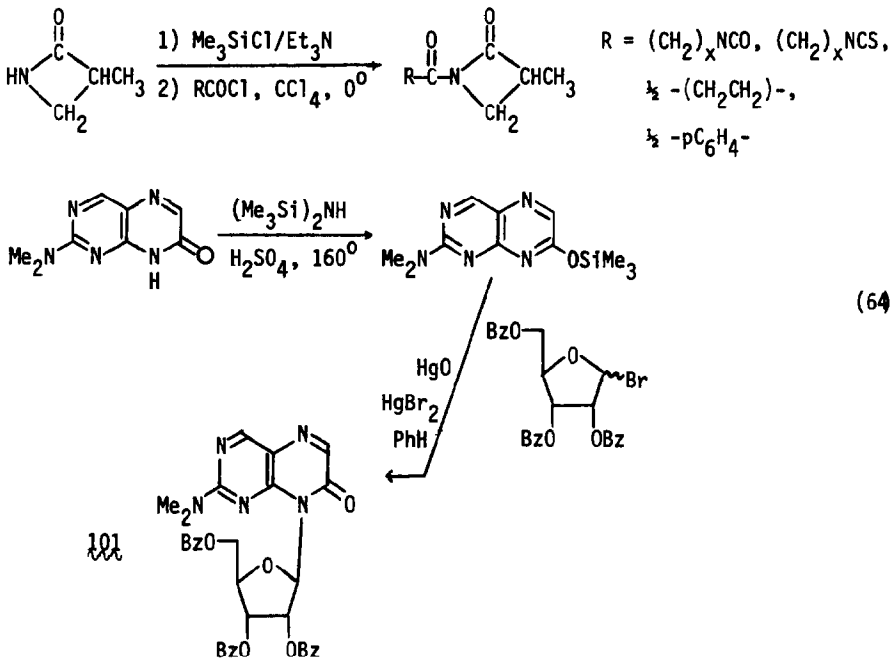
R = H for valine, = Me_3Si- for glycine, hydroxyproline, serine, tyrosine

O-H functions were converted to O-$SiMe_3$ by the silyl carbonate.

Construction of an imide linkage by N-acylation of a silyl lactam is also a feasible procedure (102,103). A variety of 5,6, and 7-membered ring lactams were acylated in high yield with α,β-unsaturated acyl halides by first activating the nitrogen by silylation, producing a variety of novel polyunsaturated imides (102)(eq. 63). In the β-lactam series similar reaction affords acylazetidinones, which undergo a number of interesting ring-opening and polymerization reactions (103). Related to this reaction is the forging of a nucleoside bond, which has been the subject of active investigation since 1964. The generality of coupling silyl nucleo-bases with sugar halides has been explored (104-106). In the pteridine series, yields were in the 30-50% range, with the example of eq. 64 (104)

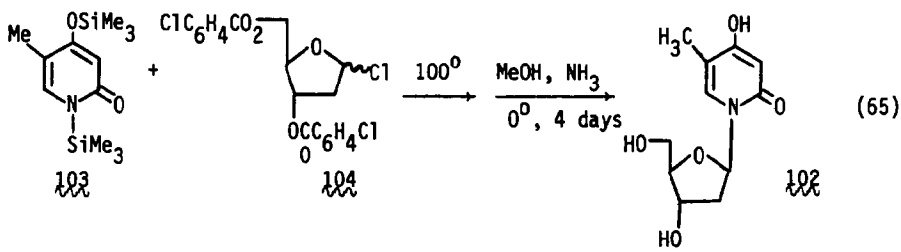


(63)



(64)

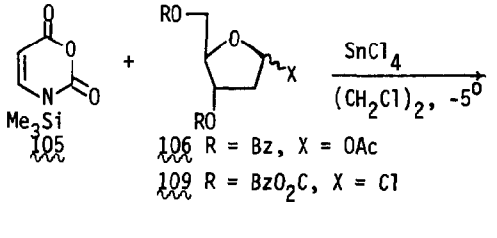
being typical. Note the use of concentrated sulfuric acid as a silylation catalyst. A new synthesis of the aberrant nucleoside 3-deazathymine 102 involved thermal coupling of siloxy pyrimidone 103 with the protected ribofuranosyl halide 104 (105). Deblocking with methanolic ammonia gave a mixture of the α- and β-anomers (eq. 65)



(65)

The silylpyrimidine-acyloxysugar fusion technique afforded the protected pyrimidine antimetabolite "3-oxadeoxyuridine" 107 when trimethylsilyloxauracil 105 (107) was condensed with sugar 106 (106) as shown in eq. 66. As the protecting groups could not be easily removed from 107 without ring-opening, the parent nucleoside 108 (which has shown anti-leukemia activity in murine screens) was

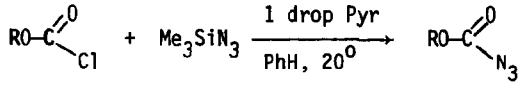
prepared by condensation of 105 with halosugar 109, followed by catalytic hydrogenation. The benzyloxycarbonyl protecting group is thus added to the arsenal of protecting functions in nucleoside chemistry (106).



(66)

Silylation also activates nitrogen functions in nucleo-bases toward simple alkylation. Bis(trimethylsilyl)thymine is alkylated by 1,2-dibromoethane or 1,4-dibromobutane at 50° (neat) in a seven day reaction period to give the 1-(ω-bromoalkyl)thymine in 55-91% yield (108).

Although trimethylsilyl azide reacts with chloroformates at 80-100°, the azidoformates produced are unstable at this temperature and react with solvent. However a catalytic amount of pyridine allows the reaction to be carried out at room temperature, producing these nitrene precursors (eq. 67) in excellent yield in a simple reaction technique (109).



(67)

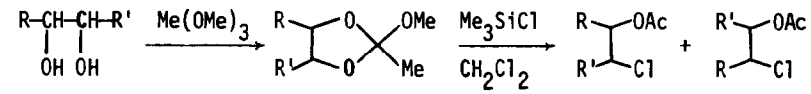
The reaction of trimethylsilyldialkylamines with aldehydes and ketones offers a route to enamines under mild conditions (ambient temperature with a trace of p-toluenesulfonic acid or heating at 70° with no catalyst) (110). This method has synthetic utility in the preparation of dimethylaminoenamines, where the traditional method utilizing gaseous dimethylamine is inconvenient (eq. 68). A limitation appears to be lessened reactivity for α-substituted carbonyls, e. g. 2-methylcyclohexanone → 1-morpholino-x-methylcyclohexene only at 70° with TsOH. No mechanism was proposed, although anionic catalysis (61) producing an intermediate gem-siloxyamine seems probable. Cyclohexanone, cyclopentanone, n-butanal and isobutyraldehyde were among the carbonyl compounds that reacted well

$$2\ Me_2NSiMe_3 + R^1\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_2R^2 \longrightarrow R^1\text{—}\underset{NMe_2}{\overset{|}{C}}\text{=}CHR^2 + Me_3SiOSiMe_3 \quad 78\text{-}88\% \qquad (68)$$

p-Dimethylsilyl, and other aromatic isocyanates, react with imidic esters (RC(OEt)=NH) with formation of N-carbamoyl imidates, $RC(OEt)=NCONHC_6H_4SiMe_2H$, a new class of reactive silanes (111).

B. Acylation and Alkylation of Oxygen

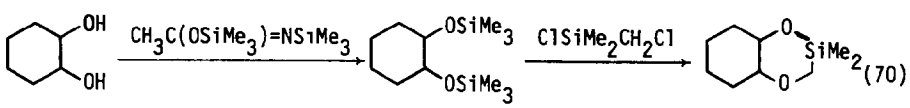
Silylation has traditionally been of slight advantage in the conversion of alcohols to esters, but has been employed in a superior method for the conversion of 1,2-diols to chlorohydrin acetates 110 communicated by Newman (112). Cyclic orthoacetate 111, obtained from the diol via ester interchange, is treated with trimethylchlorosilane, affording 110 in generally excellent yield (eq. 69). Analogous 6- and 7-membered rings, i. e. orthoacetates from 1,3- and 1,4-diols, failed to react with Me_3SiCl.



R,R' = Me, H ; Ph, H ; Me, Me 111 110 72-97%

That silylation of aromatic thioacids occurs on oxygen, affording thionoacyloxysilanes, $ArC(S)OSiMe_3$, provides a convenient functionalization for these sensitive synthetic intermendiates (113).

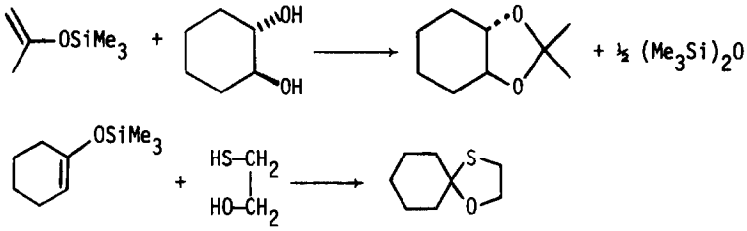
Ether synthesis by reaction of silyl ethers with primary alkyl halides is feasible (eq. 70) provided it is accompanied by ring formation (114). There is evidence that transilylation of 112 precedes cyclization to 113.



112 113

An alternative method of ketal formation, which requires no acid catalyst

is reaction of a 1,2-diol or thiol with a trimethylsilyl enol ether (115). This method of ketalization (eq. 71) may show distinct advantages in certain synthetic sequences.



(71)

Desilylation of aromatic rings with $Pb(O_2CCF_3)_4$, which can be generated *in situ* from $Pb(OAc)_4$ and CF_3CO_2H, is particularly clean, proceeding to the aryl trifluoroacetate (116). The pathway of eq. 72 is thus suggested as a convenient conversion of aryl halides to phenols under mild conditions, or for the conversion of aryl silanes to siloxanes. Lead tetraacetate by itself is a much less convenient desilylating agent.

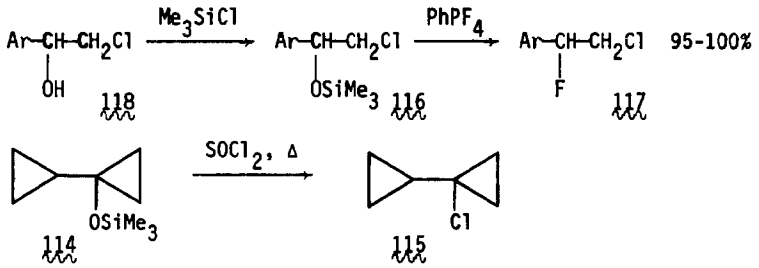
$$ArBr \xrightarrow[2)\ Me_3SiCl]{1)\ Mg} ArSiMe_3 \xrightarrow[CF_3CO_2H,\ 35^{\circ}]{Pb(O_2CCF_3)_4} ArO_2CCF_3 \xrightarrow{H_3O^+} ArOH \qquad (72)$$

Miscellaneous results concerning the formation of bonds to oxygen include the suggestion of trifluoroacetic acid as a solvent for rapid and mild silylations with $CF_3C(OSiMe_3)=NMe$ (117), and the report that silylation ($Me_3SiNHSiMe_3$, Me_3SiCl, Pyr) aided product analysis in a study of the acid-catalysed hydrolysis of ferrocenylmethylglucopyranosides (118).

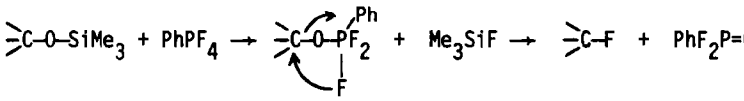
C. Formation of Other Heteroatom Bonds

Two groups (119, 120) have reported on the replacement of $-OSiMe_3$ by halogen in suitably activated systems. Siloxybicyclopropyl 114, upon treatment with thionyl chloride, was converted to 1-chlorobicyclopropyl 115 (120), while silyl chlorohydrin 116 was smoothly transformed to fluoride 117 when reacted with phenyltetrafluorophosphorane (119) (eq. 73). Interestingly chlorohydrin 118 gave only elimination products upon $PhPF_4$ treatment. In view of the known cleavage

of Si–O bonds by fluorophosphoranes (121), and the breakdown at room temperature of the oxophospholanes derived from pinacol, a multi-step, S_ni-type reaction (eq. 74) seems indicated. It will be interesting to see if $-OSiMe_3$ can be displaced from simple carbon centers, i. e. those which are neither cyclopropylcarbinyl (114) or benzyl (116) in nature.

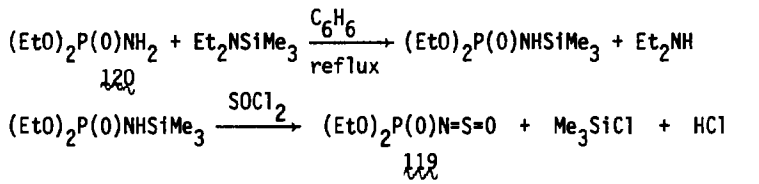


(73)



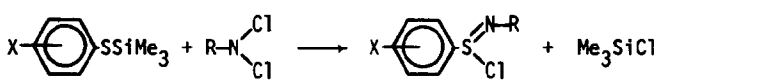
(74)

Formation of sulfur-nitrogen bonds has been the subject of two communications (122, 123). N-Sulfinyldiethylphosphoryl amide 119, a useful reagent for the synthesis of phosphoryl azomethines, is best prepared by treatment of amide 120 with diethylaminotrimethylsilane, removal of liberated diethylamine by distillation, and treatment of the residue with thionyl chloride (122) (eq. 75).



(75)

In similar vein iminosulfinyl chlorides are synthesized from trimethylsilylthiophenols and dichloroalkyl-amines and -amides (123) (eq. 76).

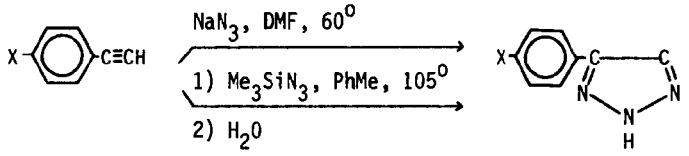


(76)

R = $ArSO_2$-, tBu-, $Me_2CC{\equiv}N$, etc. 70-98%

D. Cycloaddition Reactions

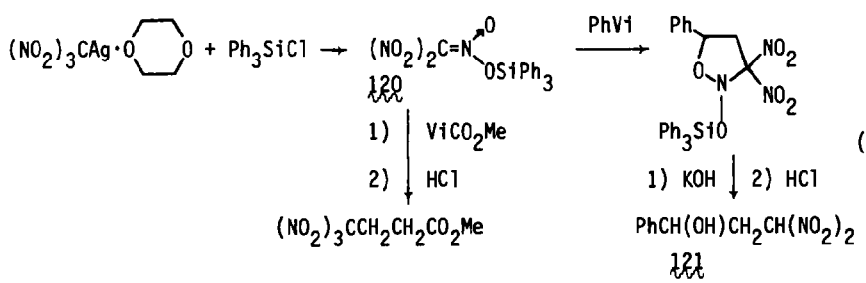
Formation of five-membered heterocyclic rings by addition of silyl azides and diazoalkanes to dipolarophiles, an active field in recent years, was the subject of lessened interest this year. A definitive paper on the synthesis of 1,2,3-triazoles (124) contrasts the trimethylsilyl azide plus acetylene synthesis with the reaction of azide ion with acetylenes in DMF (eq. 77). The two methods are complementary, in that silyl azide works best with acetylenes containing electron releasing groups, while azide ion is preferred with electron-withdrawing groups.



(77)

X =	Yield w/ NaN_3	Yield w/ Me_3SiN_3
H-	40	25
Me-	—	46
MeO-	—	18
Cl-	1	22
NO_2-	56	—

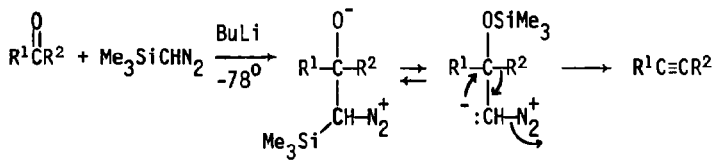
The theoretical treatment of Houk (125) should stimulate interest in silicon substituted 1,3-dipolarophiles, an example of which is the oxime-oxide 120 generated by silylation of the silver salt of trinitromethane (126), which compound cycloadds to styrene, affording, after basic hydrolysis, 1,1-dinitro-3-phenyl-3-propanol 121 (eq. 78). No cycloaddition occurs with methyl acrylate; Michael Addition intervening.



(78)

V. REARRANGEMENTS

Trimethylsilyldiazomethane, a reagent which has failed to live up to its hoped for reactivity, has found usefullness. It effects the conversion of aldehydes and ketones to the acetylene with one more carbon atom (127) in modest yield. A mechanism involving Wolff Rearrangement and silanol elimination (eq.79) was favored. Further study may improve the low yields in the alkyl series.

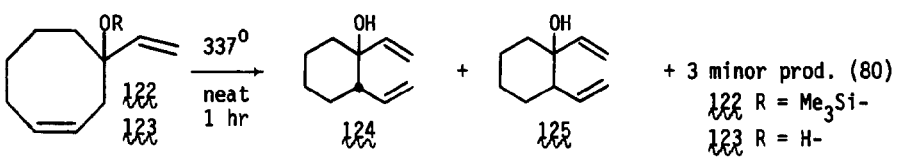


(79)

$PhCH_2CHO \rightarrow PhCH_2C{\equiv}CH$, 35% ; $PhCOMe \rightarrow PhC{\equiv}CMe$, 16% ; $(PhCO)_2 \rightarrow PhC{\equiv}CCOPh$

The manifold rearrangements of vinylsiloxycyclopropanes (to cyclobutanones, cyclopentanones, and ethyl vinyl ketones)(82) have been discussed in Section IIID.

The silicon-Cope rearrangement and similar reactions have been a continuing demonstration of the ability of silyl substitution to modify the course of an organic reaction. The siloxy-Cope rearrangement of 122 at 337° gives, after hydrolysis, significant and synthetically useful yields of 124 and 125 (128). In contrast, alcohol 123 gives principally ring-enlarged products (eq. 80).

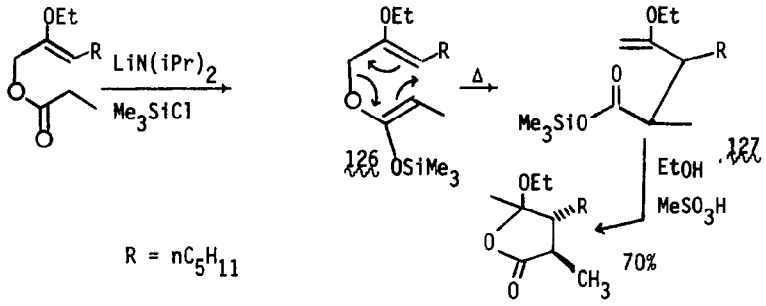


+ 3 minor prod. (80)

122 R = Me_3Si-

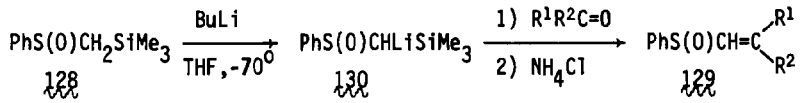
123 R = H-

The use of a silyl ketene acetal in a dihydrojasmone synthesis reported by Ireland and Mueller (129) involved a siloxy-oxa-Cope rearrangement of ketene acetal 126, yielding the thermodynamically more stable ester 127, which lactonized upon hydrolysis (eq. 81).



(81)

Ketones can be converted to vinyl sulfoxides, i. e. 128 → 129, by a process which combines the Brook rearrangement with a Wittig-type reaction (130). This is applicable to a wide variety of carbonyl compounds, and Michael addition is not a competing process with acrolein and cinnamaldehyde (eq. 82), however the

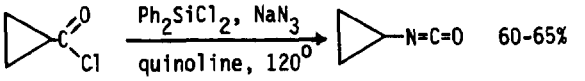


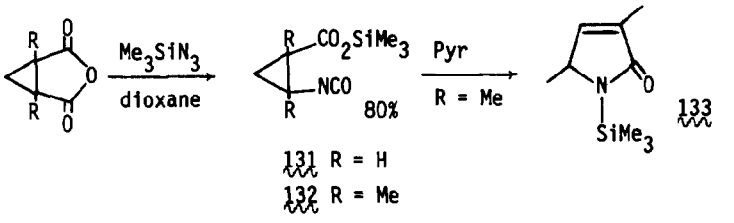
(82)

silylmethyl phenyl sulfoxide 128 is not readily available, and thus the synthetic utility this procedure offers may be marginal. Acylation of 130 with esters is feasible (→ $PhS(O)CH_2COR$), as is alkylation with methyl, but not higher alkyl, iodides.

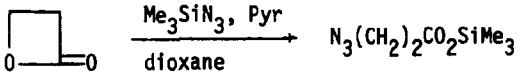
Use of trimethylsilyl azide in the Curtius and related rearrangements continues to be vigorously prosecuted (131-136). Perfluoroalkyl isocyanates are conveniently synthesized from Me_3SiN_3 and commercially available fluoroacyl halides (131), but triphenylsilyl azide fails to react. In similar vein, long-chain alkyl isocyanates are prepared in a one-pot reaction from Me_3SiN_3 and fatty acid chlorides, e. g. oleyl chloride → cis-8-heptadecenyl isocyanate (89%)(132). Cyclopropyl isocyanates are prepared in a similar reaction (133), and the highly-substituted 132 rearranges in the presence of pyridine to pyrrolinone 133. Catalysis by pyridine allows silyl-Curtius rearrangement of activated esters to proceed, e. g. $C_6Cl_5CO_2Et$ → C_6Cl_5NCO, while propiolactone and diketene suffer ring opening to silyl β-azido esters (134) as summarized in eq. 83.

$$R_fCOCl + Me_3SiN_3 \xrightarrow[\text{mesitylene}]{100^0,\ 18\ hr} R_fN{=}C{=}O \quad R_f = nC_5F_{11},\ nC_7F_{15},\ \tfrac{1}{2}\text{-}(CF_2)_3\text{-} \quad 78\text{-}89\%$$

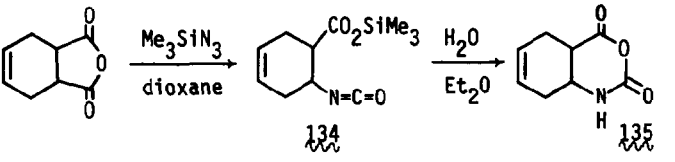




(83)

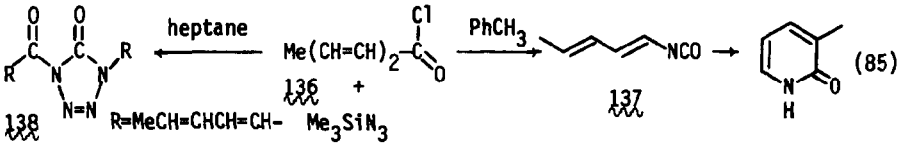


Substituted succinic anhydrides are opened to silyl β-isocyanatoesters 134 by trimethylsilyl azide (107,135), which are cyclized (with desilylation) upon hydrolysis to N-carboxyanhydrides of β-aminoacids 135 which can be polymerized to novel polyamides (135) (eq. 84).



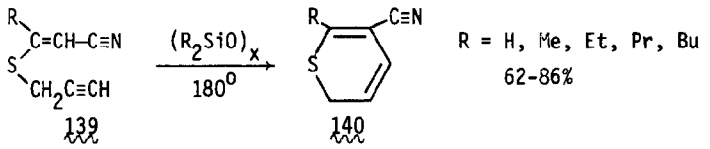
(84)

The silyl azide modification of the Curtius rearrangement applied to a toluene solution of sorboyl chloride 136 affords the sensitive 1,3-pentadienyl isocyanate 137, which undergoes electrocyclic ring closure to 3-methyl pyridone (eq. 85). In heptane the major product is the tetrazolinone 138, formed via cycloaddition of 137 and 2,4-hexadienoyl azide (136).



(85)

Where HMPT, DMSO, quinoline, and paraffin oil all failed to give the desired product, silicone oil (type unspecified) was useful as a solvent for the thermal rearrangement of propargylthioacrylonitriles 139 to cyanopyrans 140 (137) (eq. 86

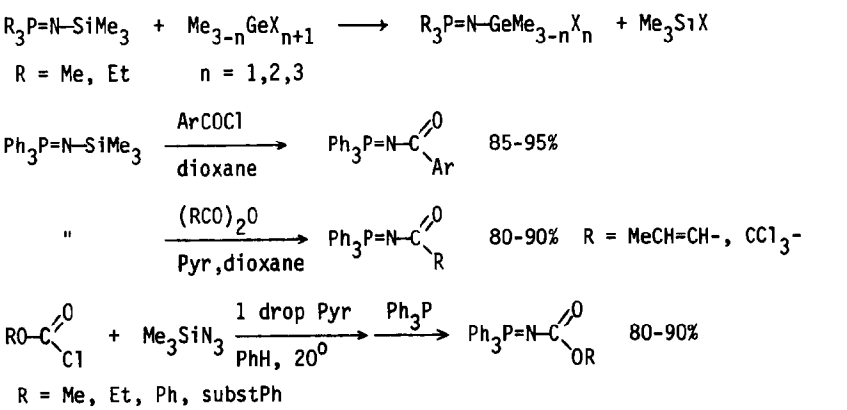


139 140

R = H, Me, Et, Pr, Bu
62-86% (86)

VI. APPLICATION TO PHOSPHORUS CHEMISTRY

The readily accessible silylphosphinimines react with chloro- and bromogermanes to yield germylphosphinimines difficult to obtain by other procedures (138). N-Acyltriphenylphosphinimes are similarly accessible is high yield reactions starting from either N-silylphosphinimines or alkoxycarbonyl azides of diverse structure (109)(eq. 87).



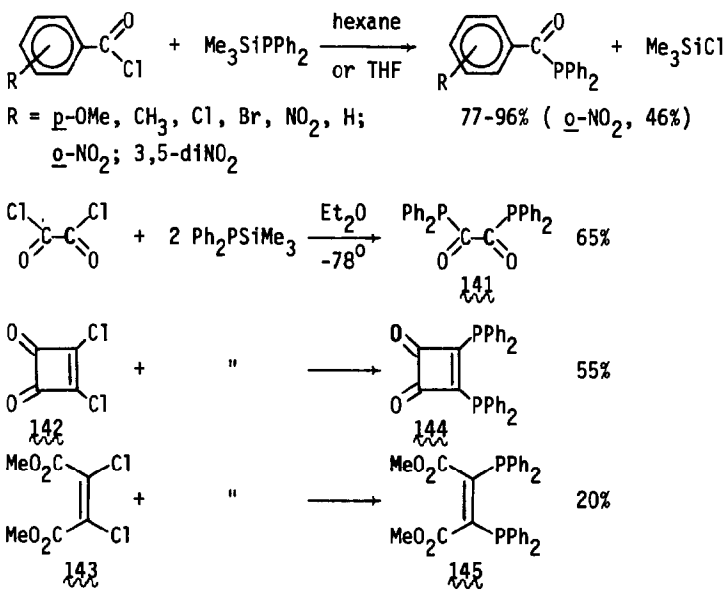
(87)

Silylphosphines are of utility in the synthesis of C–P bonds. The reaction of alkali-metal phosphides with mono- and di-acid chlorides is complicated by ketyl formation and subsequent reactions leading to products other than acyl phosphides. Because of their lesser sensitivity to oxidation and hydrolysis, their

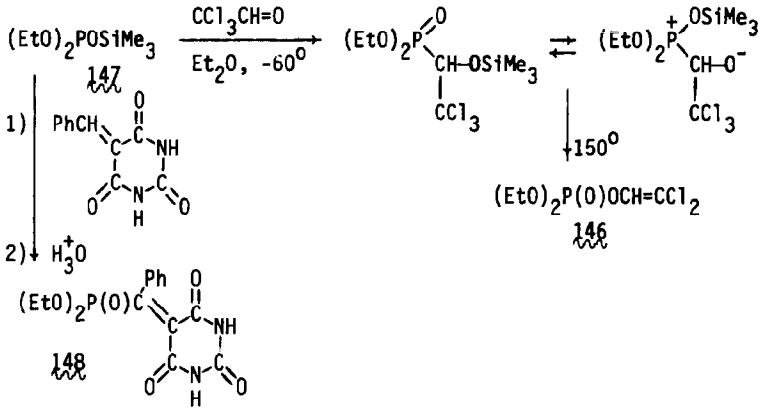
good solubility in hexane and THF, trimethylsilyldiarylphosphines are favored for the synthesis of acid phosphides (139, 140). In the aryl series, trimethylchlorosilane is easily separated, and yields are uniformly high (139). With R = p-COCl the monophosphide could be isolated and derivatized to the methyl ester or anisyl amide. Oxaloyl chloride afforded the diphosphide 141, while the vinylogous acid chlorides 142 and 143 gave the novel phosphines 144 and 145 (140)(eq. 88). Benzenesulfonyl chloride was reduced by two equivalents of Me_3SiPPh_2 to phenylthio diphenylphosphinate $Ph_2P(O)SPh$ rather than giving the sulfonyl phosphide (139).

β,β-dichlorovinyldiethyl phosphate 146 was prepared by a novel sequence involving condensation of chloral with silyl phosphite 147, and subsequent pyrolysis (eq. 89) involving a phosphonate-phosphate rearrangement (141). Phosphite 147 also added to the exocyclic double bond of benzylidene barbituric acid to give, after hydrolysis, 148 in 97% yield (142).

Dithiocatechol phosphoranes 149 are synthesized from o-bis(trimethylsilylthio)benzene and fluorophosphoranes (eq. 90). With PF_5, the phosphonium salt

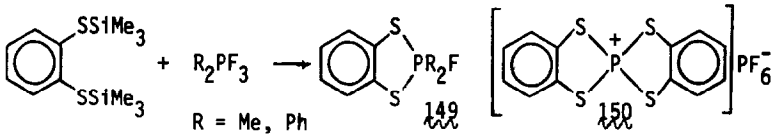


(88)



(89)

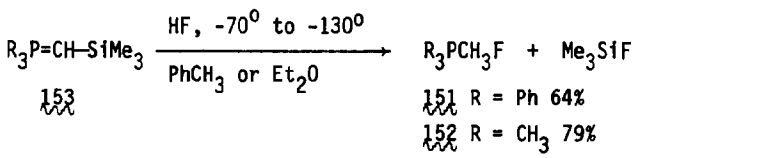
160 was obtained rather than a tetrathiophosphorane (143).



(90)

The thiophosphines $(CF_3)_2P{-}SH$ and $(CF_3)_2PSP(CF_3)_2$ can be conveniently prepared by desilylation, with HBr and $(CF_3)_2PCl$ respectively, of $(CF_3)_2P{-}SSiMe_3$, itself readily preparable from $(CF_3)_2PCl$ and bis(trimethylsilyl)sulfide (144).

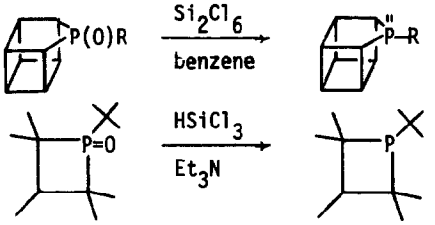
Methyltriphenylfluorophosphorane 151 and tetramethylfluorophosphorane 152 are conveniently prepared by treatment of the pure salt-free ylids 153 with hydrogen fluoride (eq. 91)(145). Ylids 153 were easier to obtain in pure form than $R_3P{=}CH_2$ (146). Interestingly, 151 exists as the pentacoordinate species while 152 appears to be the phosphonium salt $Me_4P^+F^-$ (145).



(91)

Use of Si-H bonds for the reduction of phosphorus(V) to phosphorus(III) continues to be exploited. Perfluoromethylfluorophosphoranes are rapidly reduced by Me_3SiH in the vapor phase at 25° to perfluoromethylphosphoranes, e. g. $Me_3SiH + (CF_3)_3PF_2 \rightarrow (CF_3)_3PH_2$ (147). These phosphorus(V) hydrides are quite unstable at room temperature. Eq. 92 illustrates some examples of silane reductions of phosphine oxides to phosphines (148-150).

$$PhP(O)(CH_2CH_2CH_2PPh_2)_2 \xrightarrow[\text{benzene}]{Si_2Cl_6} PhP(CH_2CH_2CH_2PPh_2)_2 \quad 86\text{-}99\% \quad \text{ref. 148}$$



Desulfurization of phosphine sulfides and thiophosphates can be accomplished by treatment with trichlorosilane and gamma rays (151). However, the low yields, e. g. $Ph_3P{=}S \rightarrow Ph_3P$: 34%, $(PhO)_3P{=}S \rightarrow (PhO)_3P$: 10%, make this method presently unattractive for synthetic purposes.

VII. SILICON AS A PROTECTING GROUP

Trialkylsilyl groups have been well utilized in synthesis as protecting functions for alcoholic, phenolic and acidic OHs. The requirements of prostaglandin synthesis have spurred interest in this area (vide supra) but first consideration should be in more general areas. The commercially available t-butyldimethylchloro silane has been investigated for protecting nucleoside hydroxyl functions during synthetic and sequencing studies (152). Advantages are: 1) selective derivitization of the 5'-position with $tBuMe_2SiCl$/imidazole/DMF, 2) stability of derivatives to base (9 N NH_4OH, 60% recovery) or to hydrazine, which removes the commonly used β-benzoylpropionyl group, 3) facile cleavage of $tBuMe_2Si$– with 80% HOAc or Bu_4NF (153,154), and/or 0.5 N ethanolic NaOH, and 4) production of characteristic mass spectral fragmentation patterns in the nucleoside derivatives.

As examples of the inertness of trialkylsilyl groups to standard reactions, it may be noted that the trimethylsilyl ether of 10-undecyn-1-ol survived hydroboration, treatment with a lithium acetylide, iodine in THF, and 3 N NaOH (155) in a synthesis of the insect phemerone bombykol (1-hexadeca-10(E),12(Z)-dienol. Interestingly, trimethylsilyl removal was effected with isobutyric acid (→ isobutyrate ester) followed by LAH reduction (155).

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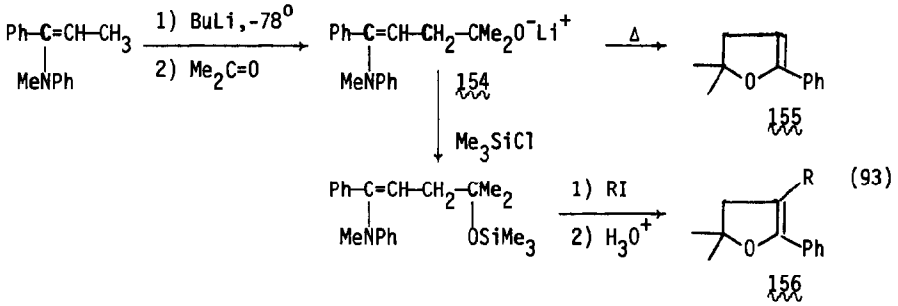
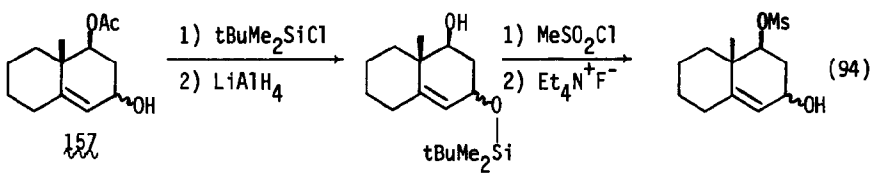
A novel example of the protection by silyl groups is the observation that 4- and 5-hydroxy enamines, e. g. 154, prepared by alkylation of metallated enamines, condense to the synthetically less useful dihydro-furans and -pyrans, e. g. 155, upon warming. The alcohol function is deactivated by condensation of the initially obtained lithium alkoxide with trimethylchlorosilane, allowing further alkylation of the amine. The net result allows synthetic use of Michael addition with reversed polarity. The example in eq. 93 is instructive on the possibilities of this technique (156).



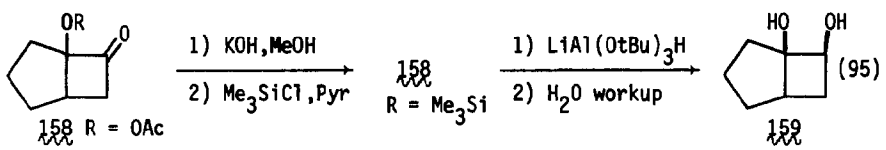
(93)

The t-butyldimethylsilyl function (153) was used as a protecting group for the sensitive allylic alcohol 157 in order to avoid di-mesylation in the following sequence (eq. 94)(157). Similarly, the alcohol function in the bicyclo(3.2.0)hep-



(94)

tane 158 was protected as a trimethylsilyl ether during hydride reduction to the cis-diol 159 (eq. 95)(158).

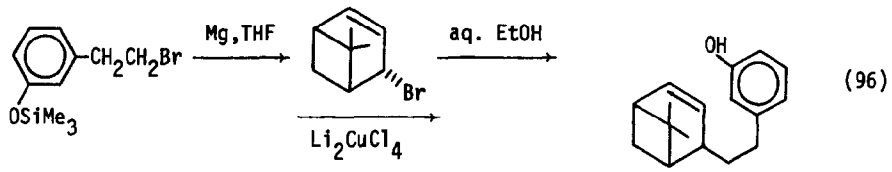


(95)

Androst-5-ene-3β,17β-diol was selectively silylated at the 3-position, allowing oxidation at the 17-position (CrO_3-Pyr). Desilylation ($Bu_4N^+F^-$ or AcOH-H_2O-

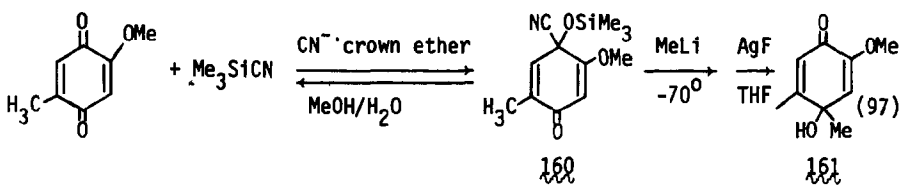
THF) yielded dehydroisoandosterone (androst-5-ene-3β-ol-17-one) in 65% overall yield (159). Silylation should not however, be considered a panacea, for in an epi-allogibberic acid synthesis, protection of an -OH function as the trimethylsilyl ether during a basic hydrolysis step failed (160), and the tetrahydropyranyl ether was employed instead.

The example of eq. 96 demonstrates how a phenolic group may be protected during a cuprate-induced coupling (161).



(96)

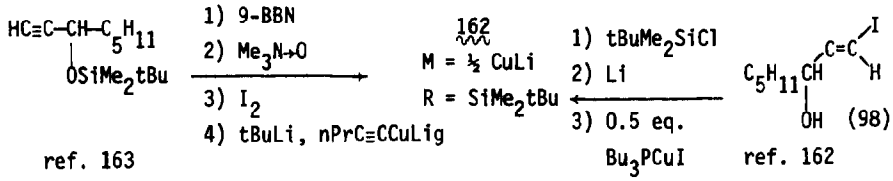
The reaction of trimethylsilyl cyanide with quinones provides a specific blocking group for the nucleo- and electro-philicly labile quinone function (62). Admixture of the neat reagents in the presence of a catalyst affords the siloxynitrile, e. g. 160, in 65-95% yield. The more electrophilic carbonyl center of the quinone is selectively silylated (eq. 97). 160 Can be reacted with an alkyl lithium to form the difficultly accessible quinols, e. g. 161, as the unprotected dienone carbonyl now exhibits enhanced reactivity. The siloxy nitrile moiety is rapidly transformed to carbonyl by both nucleophiles (F^-) or electrophiles.



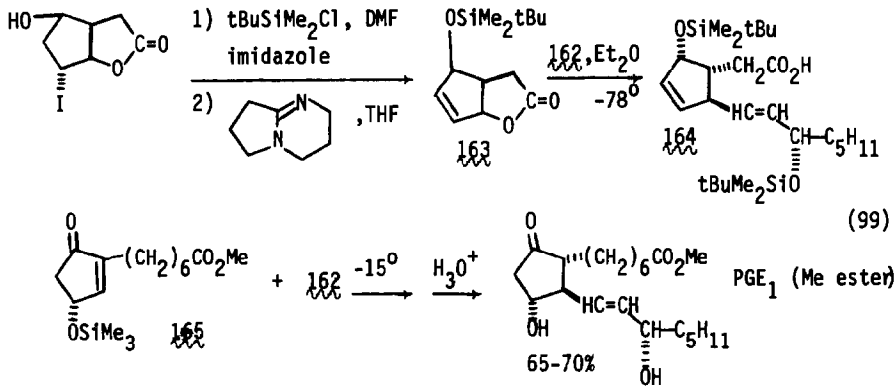
(97)

160 161

The field of prostaglandin synthesis has perhaps made the greatest use of silicon reagents as blocking functions. Central to this synthetic activity is the vinyl metallic 162, M-CH=CH-CH(OR)C_5H_{11} (162-164), the synthesis of which is outlined in eq. 98. Coupling of 162 with the silylated lactone 163 produces the

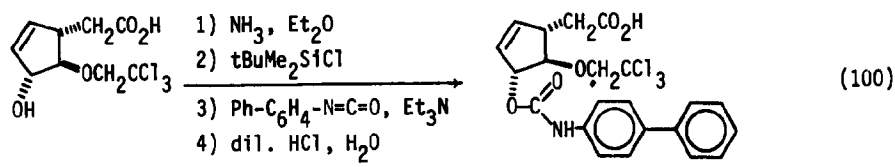


blocked intermediate 164 (163) (eq. 99). Alternatively, coupling with cyclopentenone 165, gives after hydrolysis prostaglandin E_1 methyl ester (162) (eq. 99).



162: R = Me_2tBuSi, M = Li, found application as well in the synthesis of 8-methyl-prostaglandin C_2 (164).

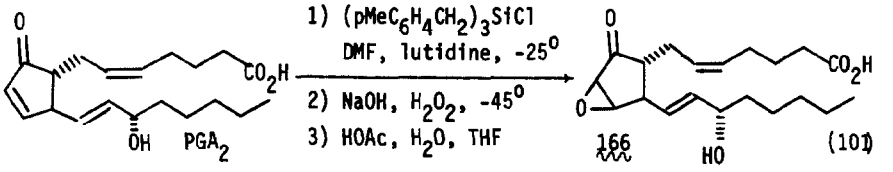
In a synthesis of an intermediate to become the prostaglandin five-membered ring, t-butyldimethylchlorosilane was used to protect a carboxyl group during the conversion of an alcohol to a urethane (165) (eq. 100).



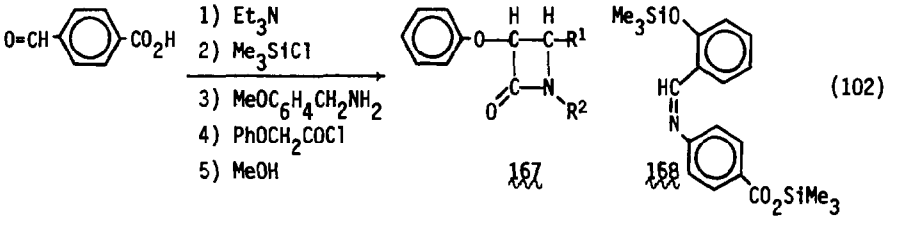
(100)

Stereoselective epoxidation of prostaglandin A_2 is a matter of continuing interest (166,167). Disilylation of the acid and alcohol functions of PGA_2 increased the α:β ratio of epoxides formed in subsequent steps, leading to an over 40% yield of the most biologically active prostaglandin (PGE_2) from PGA_2 isolated from the common Caribbean sea whip (166). The silyl groups disappeared in the aqueous workup. A more novel approach to direct epoxidation to the α-face specif-

ically involves attachment of a "remote-controller" to the C-15 oxygen. The tri-p-xylylsilyl moiety is large enough to block the β-face, giving a 94:6 ratio of α- and β-10,11-epoxy-PGAs, 166, of which the former is shown in eq. 101 (167).



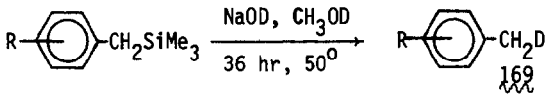
The stability of trimethylsiloxy alcohols and esters to basic conditions, coupled with their easy cleavage under mild treatment (methanol, or 95% ethanol), makes silylation a superior protection for alcohol and carboxylate functions. This was exploited in a one-pot synthesis of β-lactam penicillin analogs (168). Benzylaldehyde-4-carboxylic acid in methylene chloride was treated sequentially with triethylamine, trimethylchloro silane, p-methoxybenzyl amine, phenoxyacetyl-chloride, and methanol, yielding 75% of β-lactam 167 (R^1 = p-$HO_2CC_6H_4$, R^2 = p-$MeOC_6H_4CH_2$). Condensation of the disilylated Schiff base 168 with phenoxy-acetyl chloride/triethyl amine followed by methanolic workup gave 167 (R^1 = o-HOC_6H_4, R^2 = p-$HO_2CC_6H_4$) in 89% yield (eq. 102). A β-lactam was also obtained when $MeOC_6H_4CH{=}NC_6H_4CO_2SiMe_3$ was coupled with the mixed anhydride $N_3CH_2CO_2COCF_3$ in similar fashion (169).



(102)

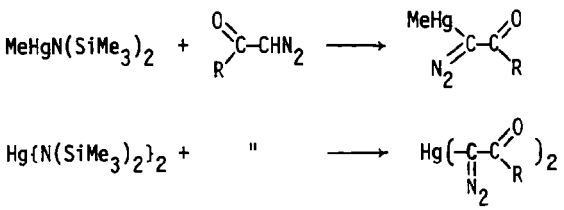
A caveat to the use of trimethylsilyl ethers as protecting groups for OH: Alkoxytrimethylsilanes (RO- = OiPr, OEt) undergo slow hydrogenolysis over a palladium on carbon catalyst at 1 atm. (170).

Some synthetic application of the protodesilylation reaction, i.e. cleavage of the carbon-silicon bond, has been made, particularly for the synthesis of specifically deuterated compounds (171-172). The apparent method of choice for the preparation of α-deuterotoluenes is deutero-desilylation of benzyltrimethylsilanes (eq. 103). Even with the deactivating m-CF_3 substituent, 169 (R = m-CF_3) was isolated in 98% isotopic purity (171). Of related interest is the report that cis- or trans-β-deuteriostyrene is obtained in >96% stereochemical purity by deuterolysis of cis- or trans-β-trimethylsilylstyrene with DCl in acetonitrile at reflux (172).



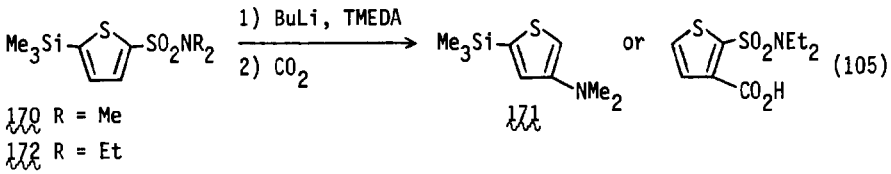
(103)

For the preparation of organomercury diazoketones, a silylamine route is preferred (173). Ethylmercuri, methylmercuri, and mercuric salts of hexamethyldisilazane react with diazoalkanes (produced e. g. in the Arndt-Eistert synthesis) in ether solution, yielding these derivatives in nearly quantitative yield (eq. 104). This technique constitutes a valuable synthetic procedure for functionalization of the diazo group.



(104)

The trimethylsilyl group is not an effective group for blocking matalation α to sulfur in 2-sulfonamidothiophenes as it can not be removed by acid hydrolysis. Metallation of 170 and subsequent carbonation gave only rearranged amine 171, while 172 lost the silyl group under the reaction conditions (174)(eq. 105).



170 R = Me
172 R = Et

171

Triethylsilyl radicals generated by photolysis of triethylsilane effectively abstract Br· from alkyl halides to generate radicals for esr studies (175-176). Similarly, solutions of trimethylsilyl sodium in HMPT act as effective one-electron transfer agents to produce radical anions suitable for esr investigation from a variety of compounds, e. g. naphthalene, fluorene, benzophenone (177).

Application of silyl-ω-isothiocyanatoalkyl carboxylates to polyamide synthesis has been reported (178-179).

Kinetic studies of the synthetically useful preparation of tin hydrides *via* Si-H/Sn-O exchange, i. e. $R_3SiH + R'_3SnOR'' \longrightarrow R_3SiOR'' + R'_3SnH$, have been made and analysed (180).

The synthesis of polynuclear manganese carbonyls and manganese carbonyl phosphines is mediated by chlorosilanes. Curtis isolated $(Et_4N)(Mn_3(CO)_{14})$ (181) from reaction of triphenylchlorosilane with sodio manganese pentacarbonyl in THF. The first example of a chelating acetate ligand in a metal carbonyl, $(CH_3CO_2)Mn(CO)_2(PPh_3)_2$ 173, was accidently synthesized by the Treichel group (182). $NaMn(CO)_5$ treated sequentially with 1 eq. of Me_3SiCl and 4 eq. of Ph_3P in acetic acid afforded 173 together with $Mn_2(CO)_9PPh_3$ and $Mn(CO)_3(PPh_3)_2Cl$. The mechanism of this transformation is presumed to involve oligomerization of $R_3SiMn(CO)_5$ to the $Mn_3(CO)_{14}^-$ anion, followed by attack on the latter by PPh_3, HCl, and HOAc.

A novel preparation of the *ortho*-metallated rhodium complex, tetrahapto-$(Ph_3P)_2Rh(o\text{-}C_6H_4PPh_2)$ in greater than 90% yield involves treatment of $(Ph_3P)_3RhCl$ with Me_3SiCH_2Li or Me_3SiCH_2MgI (183). As Me_4Si is the other product, it is assumed that an intermediate silylmethyl-rhodium species undergoes oxidative addition and subsequent elimination.

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