THIOSILANES AS THIOKETALIZATION REAGENTS

Thesis by

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Abstract

Thiosilanes react efficiently with simple aldehydes and ketones when catalyzed with ZnI_2 to produce thioacetals and thioketals. Steroidal diketones were thioketalized with yields and selectivity superior to other methods when allowed to react with thiosilanes and ZnI_2.

The overall thioketalization process proceeds through silylhemithioketal intermediates which can be detected and isolated from the reaction mixtures. The isolated silylhemithioketals can be resubmitted to the thioketalization reaction conditions and be converted to thioketals.

List of Abbreviations

TMS	trimethylsilyl
Et	ethyl
Me	methyl
Bu	butyl
Ts	p-toluenesulfonic
Ac	acetate

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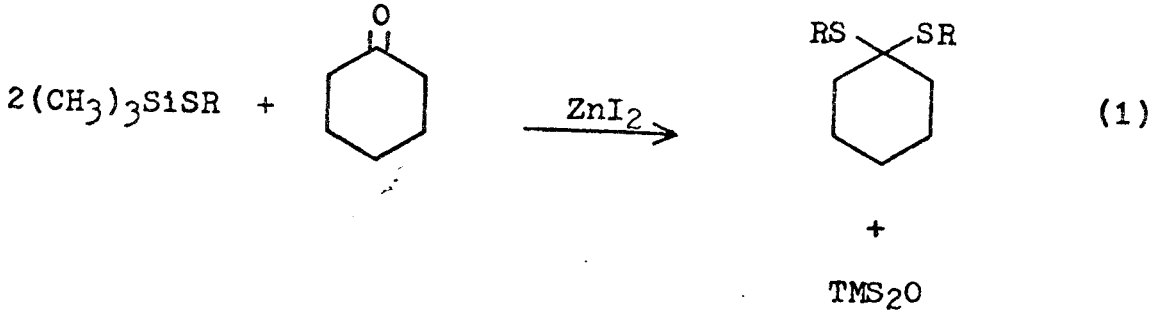
INTRODUCTION

Aldehydes and ketones are among the most important functional groups in organic chemistry. Because of the extensive use of aldehydes and ketones in synthetic work, it has occasionally become necessary to temporarily limit the reactivity of the carbonyl group during a segment of a synthetic procedure. For this reason, a wide variety of protecting groups have been developed of which thioacetals and thioketals are important members. Thioacetals have also been used to extend the reactivity of aldehydes by reversing the normal electrophilic nature of the carbonyl carbon atom to that of a nucleophilic center. This umpolung [1] or charge affinity inversion [2] of aldehydes has been studied by Seebach[1] and others[2,3].

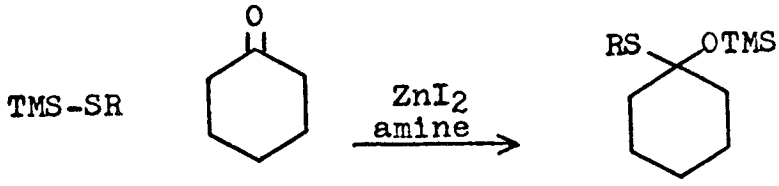
A new, mild and efficient procedure for thioketalization has been developed in which a ketone or an aldehyde is reacted with an excess of a thiosilane and a catalytic amount[4,5] of ZnI_2 (eq. 1).



(1)

The presence of amines inhibits the formation of thioketals and if the thiosilanes are contaminated with amines, only O-trimethylsilyl-S-alkylthiohemiketals, the suspected reaction intermediates, are

produced (eq. 2).



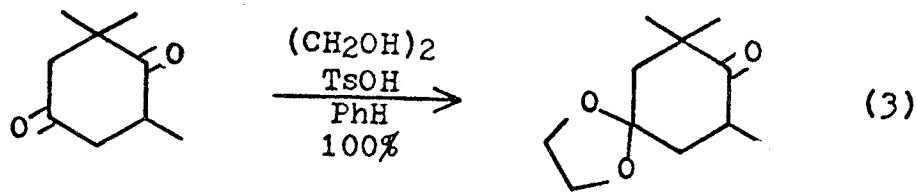
(2)

PROTECTION OF ALDEHYDES AND KETONES

Several excellent reviews [6-11] are available on aldehyde and ketone protection; only the most commonly used protecting groups will be described in this report.

1,3-Dioxalanes are the most widely used carbonyl protecting groups because they are both easily prepared and stable to a wide variety of reaction conditions, both basic and mildly acidic.

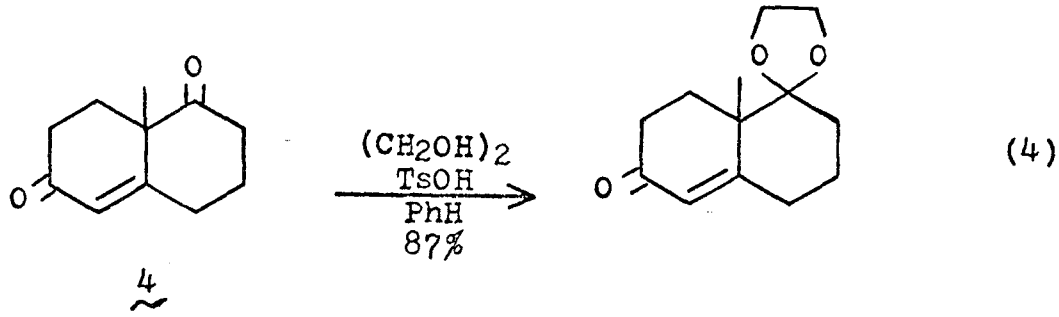
Structural and electronic differences between various ketones and aldehydes create differences in the rates of reaction and allow for selective ketalization. Isler [12] selectively protected 2,2,6-trimethyl-1,4-cyclohexanedione, 2, at the less sterically hindered carbonyl to produce the dioxalane derivative, 3, (eq. 3).



(3)

2 3

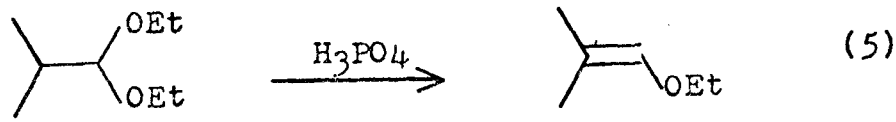
McMurray [13] has protected the Wieland-Miescher ketone, 4, at the more reactive, saturated carbonyl and thus, has illustrated the use of electronic differences to selectively ketalize carbonyl groups (eq. 4).



4 (4)

A plethora of other alcohols have been used to form both cyclic and acyclic ketals with aldehydes and unhindered ketones. However, hindered ketones can be ketalized only with glycols[11].

Acyclic acetals and ketals can eliminate a molecule of the corresponding alcohol and form enol ethers at higher temperatures[14] or under the influence of strong acids[15]. The diethyl ketal of isobutraldehyde, for example, loses a molecule of ethyl alcohol upon treatment with phosphoric acid (eq. 5)[15].

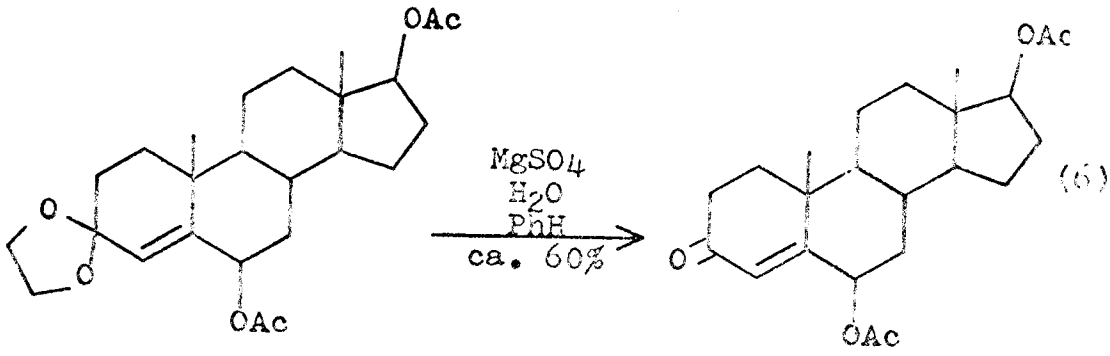


(5)

Acetals and ketals are prepared from the parent carbonyl compound by reaction with the appropriate alcohol or glycol, which is generally the solvent, and an acid catalyst such as $SnCl_4$[16], $p\text{-}CH_3C_6H_4SO_3H$ [17-21], or $BF_3 \cdot Et_2O$ [22,23]. The water generated

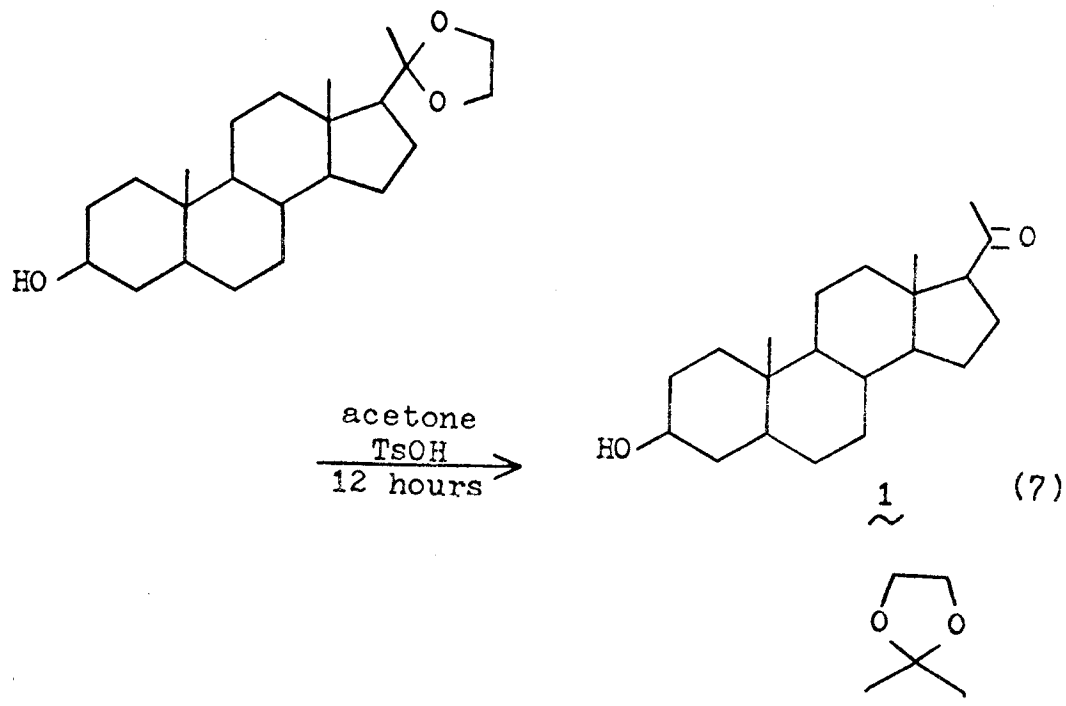
during ketalization must be constantly removed to insure complete reaction. The dehydration has been accomplished by azeotropic distillation [24,25], molecular sieves [26], and N,N'-dicyclohexylcarbodiimide[27].

Ketals and acetals are most commonly cleaved by treatment with aqueous acid [19,20,28] but the specific conditions are often system dependent. The Δ^4-3-ethyleneketal of 6β-hydroxytestosterone-6,17-diacetate was hydrolyzed by reaction with magnesium sulfate in wet benzene (eq. 6) [29].



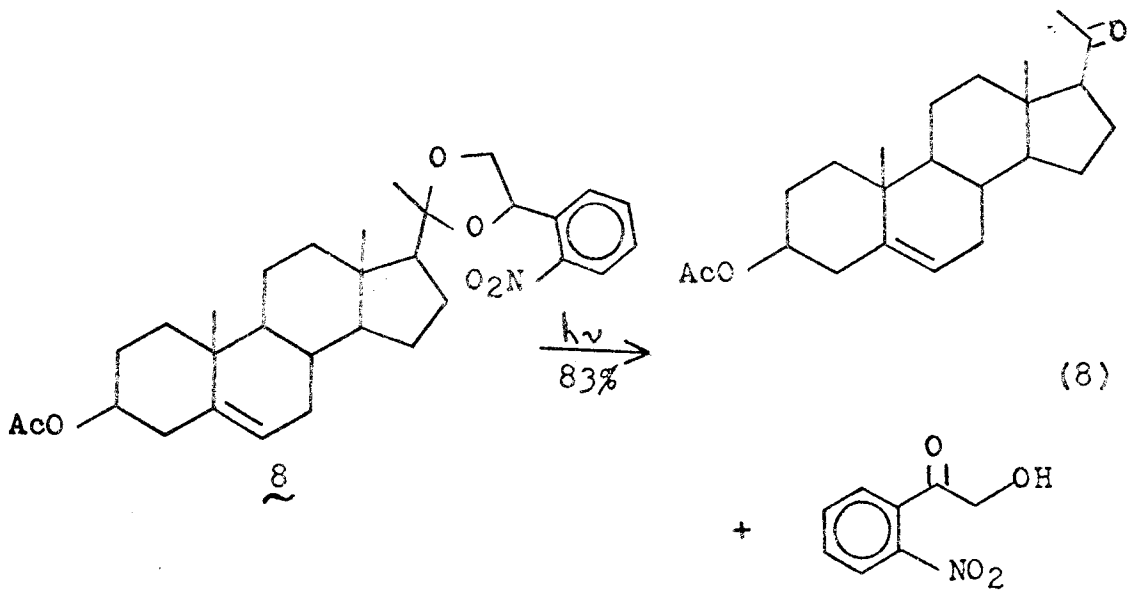
(6)

A number of alternate procedures for ketal hydrolysis have been developed. Djerassi[30] has employed an exchange technique with acetone in the hydrolysis of the steroidal ketal, 5. The acetone is converted to 1,1-dimethyldioxalane, 7, and the ketal is converted to progesterol, 1, (eq. 7).



(7)

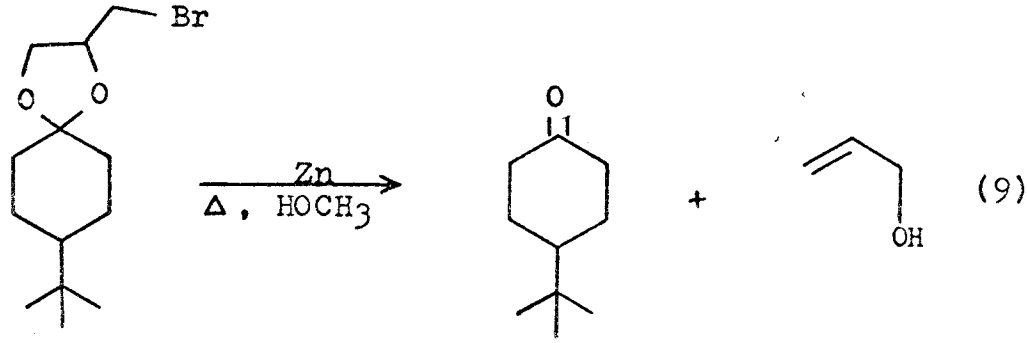
Hebart and Gravel [31] have hydrolyzed the aryl nitro substituted dioxalane of 5-pregen-3β-ol-20-one acetate, 8, photolytically (eq. 8).



(8)

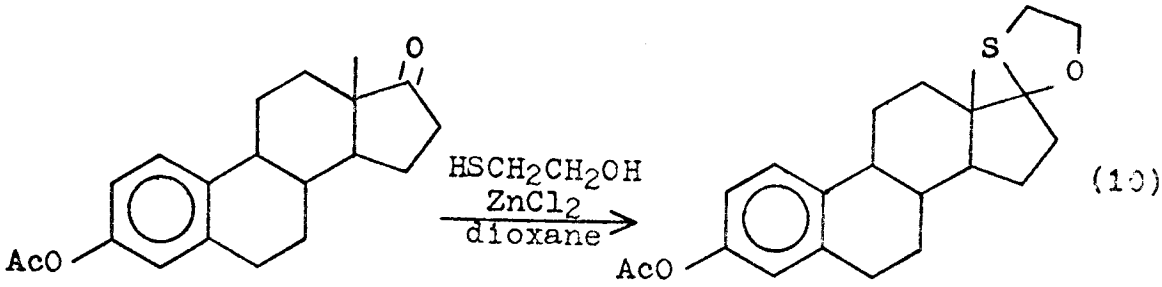
5-Pregen-3 -ol-20-one acetate, 1, was produced in an 83% yield along with the by-product, ∝-hydroxy-o-nitroacetophenone.

The bromo substituted ethylene ketal of 4-tert-butylcyclohexanone, 9, was hydrolyzed when treated with activated zinc metal in refluxing methanol. The ketone, 4-tert-butylcyclohexane, 10, was formed in an 89% yield along with the by-product, allyl bromide (eq. 9) [32,33].



9 10

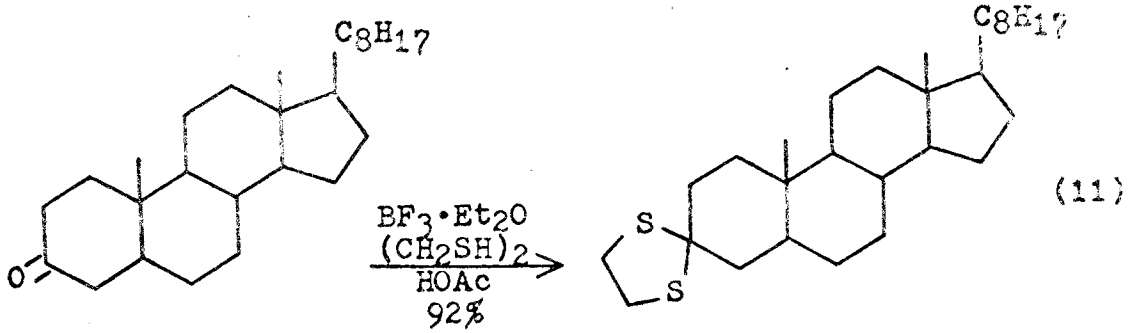
The hemithioketals represent a related class of protecting groups which, in general, may be formed under milder conditions than the thioketals. The hemithioketals are also stable to both basic and acidic reaction media. Estrone acetate, 11, has been converted to the corresponding 17-ethylenehemithioketal, 18, by reaction with β-mercaptoethanol and $ZnCl_2$ (eq. 10) [34].



11 (10) 18

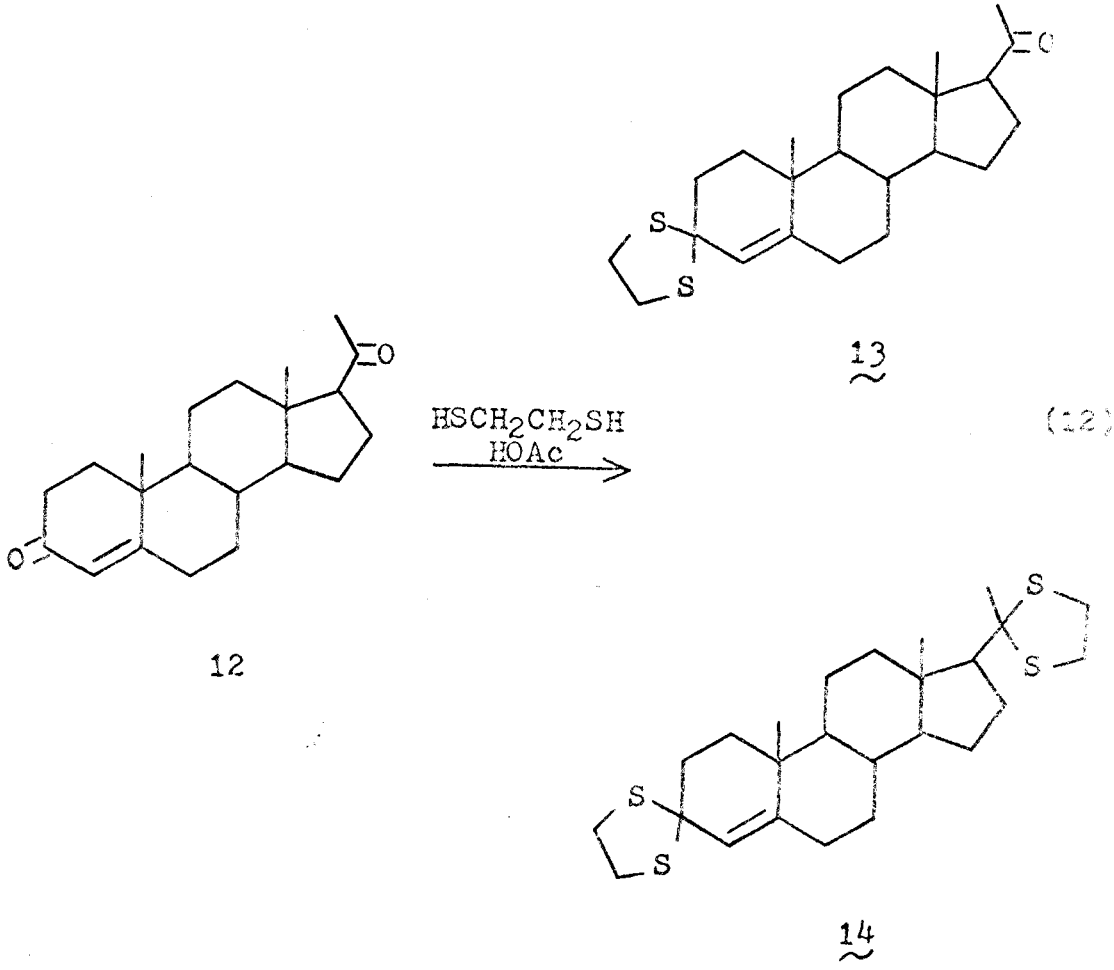
Hemithioketals are hydrolyzed by reaction with mineral acids in alcoholic solvents or dioxane (35).

Dithioketals are stable to most basic and acidic reaction conditions. The dithioketals are prepared from the parent ketone by reaction with alkyl thiols and $ZnCl_2$ (36,37), HCl (38-41), $BF_3 \cdot Et_2O$ (43) or $p\text{-}CH_3C_6H_4SO_3H$ (42). Fieser (43) has converted cholestane-3-one, 19, to the 1,2-dithiolane derivative, 20, in a 92% yield (eq. 11).



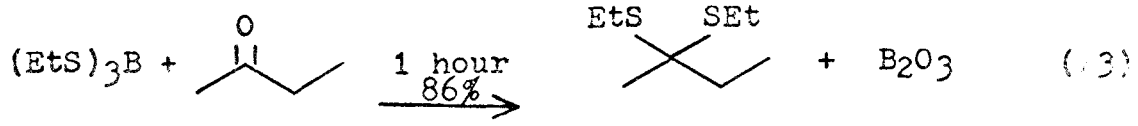
19 (11) 20

Selective protection is also possible in thioketalization reactions. Rall[33] has thioketalized progesterone, 12, to form a mixture of thioketals and shown that α,β -unsaturated ketones are more reactive toward thioketalization than are saturated ketones. The 3-ethylenethioketal of progesterone, 13, was the major product and the bis-3,20-ethylenethioketal of progesterone, 14, was the minor product (eq. 12).



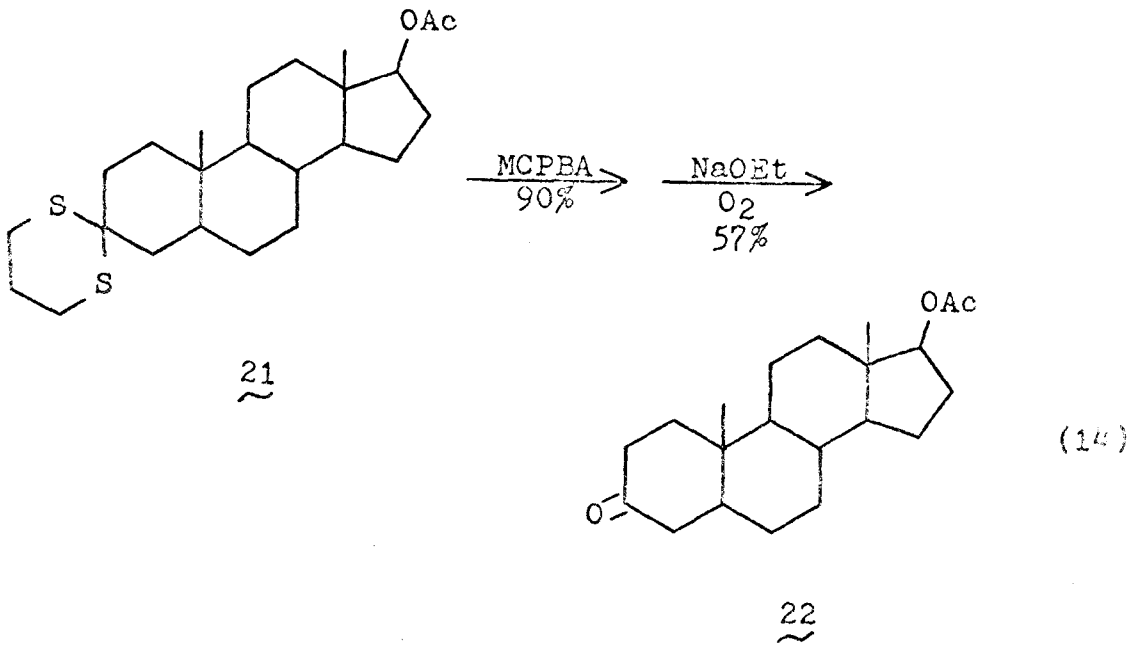
12 13 14 (12)

A novel method for the preparation of dithioketals has recently been developed by LaLancette [39,40]; however, only acyclic thioketals can be made by this procedure. An alkyl orthothioborate was allowed to react with a ketone or aldehyde to produce the product thioketal or thioacetal. 2-Butanone was converted to 2,2-diethylthiobutane and boric oxide with triethylorthothioborate by this procedure (eq. 13).



(13)

The conversion of thioketals and thioacetals to the parent ketones and aldehydes has proven to be a challenging task. Mercuric salts and aqueous acid [41,47], although the common reagents for thioketal hydrolysis, have often given quite disappointing results, although some modifications of this procedure have resulted in improved yields [48]. Several new methods of hydrolysis have recently been developed which are milder and more efficient than the mercuric salt treatment; however, these new methods are often not very general. Peracid oxidation of the 3-trimethylenethioketal of 3-keto-17-hydroxy-androstane acetate, 21, to the bis sulfoxide, followed by treatment with NaOEt gave 3-keto-17-hydroxyandrostane acetate, 22, in a 51% yield (eq. 14) [49].



21 (14) 22

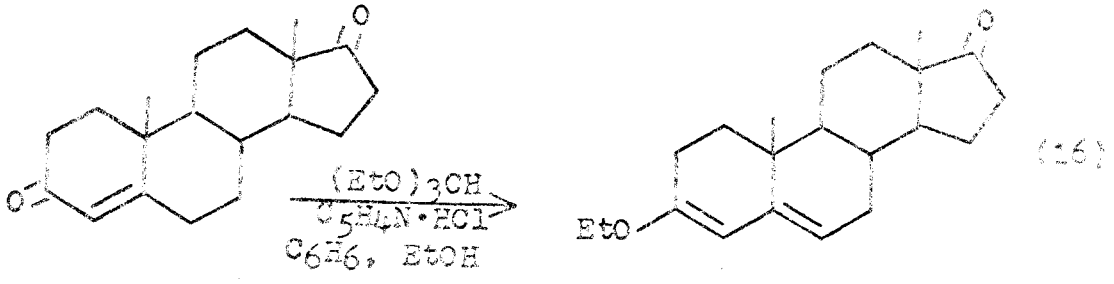
Several other oxidizing agents have been employed in similar hydrolysis procedures [50-52]. Chloromine T in aqueous alcoholic solutions have been used to convert spiro[1,3-dithane-2,9'-fluorene] to 9-fluorenone in an 86% yield [53,54]. Oxidation of dithioketals to the monosulfoxide and subsequent treatment with a catalytic amount of sulfuric acid produces the parent ketone. The dimethylthioacetal of 2-phenylethanol was converted to the monosulfoxide and treated with sulfuric acid, 2-phenylethanol resulted (eq. 15) [49,50].

$$PhCH_2CH(SCH_3)_2 \xrightarrow{MCPBA} \xrightarrow[\text{acid}]{\text{sulfuric}} \underset{88\%}{PhCH_2CHO} \quad (15)$$

Silver oxide in aqueous acetonitrile has also been used to hydrolyze

thioketals in good yields[57]. Oishi and Kamemoto [58] have studied the hydrolysis of thioketals by treatment with triethyloxonium tetrafluoroborate and aqueous $CuSO_4$. Cyclohexanone ethylenethioketal has been hydrolyzed by this procedure to give cyclohexanone in an 81% yield.

Enol ethers and thioenol ethers represent yet another class of carbonyl protecting groups. Because α,β-unsaturated ketones and α,β-unsaturated aldehydes form enol ethers more readily than saturated ketones, selective protection can occur. Djerassi[59] has prepared the ethylenol ether of androsteredione, 24, in a 60% yield (eq. 16).



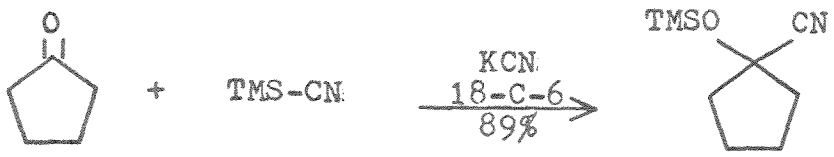
(16)

23 24

Enol ethers are stable to almost all non-acidic reaction conditions but they are readily cleaved by even mild treatment with acids.

Timethylsilylcyanohydrin derivatives are easily prepared from

ketones and aldehydes by their reaction with TMS-CN in the presence of KCN•18-crown-6 complex [60-62]. Cyclopentanone was converted to



(16)

1-trimethylsiloxy-1-cyanocyclopentane in an 89% yield (eq. 11) by this procedure. The silylcyanohydrins are hydrolyzed by treatment with AgF. This regenerates the parent carbonyl compound and forms TMS-F and AgCN.

Numerous other funtionalities have been used as carbonyl protecting groups. For example, semicarbazone oximes and hydrazones are carbonyl protecting groups but their resistance to hydrolysis greatly restricts their use. The ketals and thioketals are, however, the most often used protecting groups for ketones and aldehydes and the thiosilane procedure for thioketalization is a milder alternative for carbonyl derivatization.

RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Summary

Aldehydes and ketones have been converted to thioacetals and thioketals, respectively, in excellent yields when allowed to react with an excess of a thiosilane and a catalytic amount [63] of ZnI_2 (Table I). Several steroidal diketones have been selectively protected at the α,β-unsaturated ketone in yields and with selectivity superior to that previously reported [33]. The mechanism of the thioketalization reaction has been investigated and the intermediates are believed to be silylthiohemiketals. This thioketalization procedure is among the most gentle known and should prove useful in synthetic applications.

Preparation of the Thiosilanes

A wide variety of alkyl and aryl thiotrimethylsilanes have been prepared by allowing the corresponding sodium thiolates to react with chlorotrimethylsilane [64,65]. The ethylthiotrimethylsilane, 38, used in this report was successfully prepared by this procedure.

Table I. Preparation of Thioketals and Thioacetals by Reaction with Thiosilanes[a].

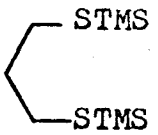
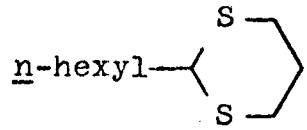
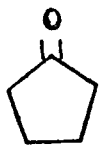
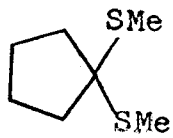
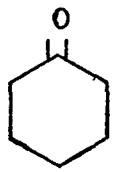
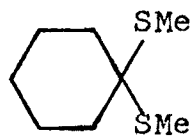
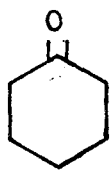
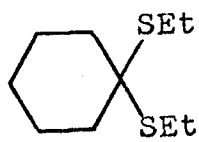
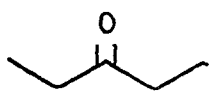
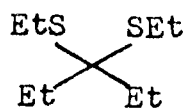
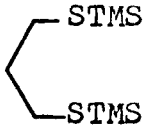
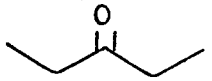
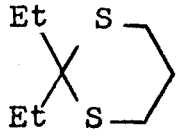
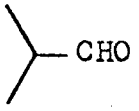
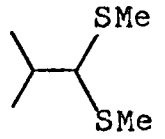
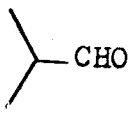
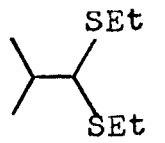
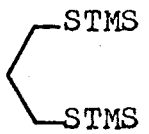
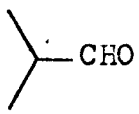
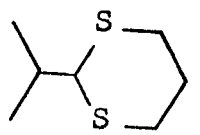
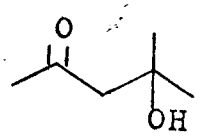
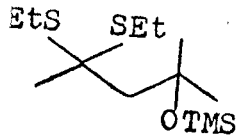
RS-TMS[b]	carbonyl compound	product	yield (%)	reaction time (hours)
R = Me	heptanal	n-hexyl-CH(SMe)$_2$	93	12
R = Et	heptanal	n-hexyl-CH(SEt)$_2$	92	24
	heptanal		75	24
R = Me			93	24
R = Me			92	18
R = Et			98	24
R = Et			91	12

Table I (continued). Preparation of Thioketals and Thioacetals by Reaction with Thiosilanes[a].

RS-TMS[b]	carbonyl compound	product	yield (%)	reaction time (hours)
			95	24
R = Me	$PhCOCH_3$	$PhC(SMe)_2CH_3$	78	72
R = Et	$PhCOCH_3$	$PhC(SEt)_2CH_3$	93	24
R = Me			85	24
R = Et			92	24
			70	24
R = Et			92	24

[a]All reactions were catalyzed with ZnI_2. [b]A 10% excess of the thiosilane was employed in all reactions.

$$EtSH \xrightarrow[Ether]{NaH} EtSNa + H_2 \xrightarrow[68\%]{TMSCl} TMS\text{-}SEt \quad (18)$$

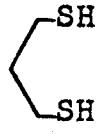
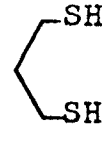
Lithium thiolates, prepared from the thiol and n-butyllithium, have also been silylated with chlorotrimethylsilane. The thiosilanes of 1,2-ethanedithiol, 1,3-propanedithiol and methanethiol were prepared by this procedure in moderate yields (eq. 19).

$$\begin{bmatrix} SH \\ SH \end{bmatrix} + n\text{-BuLi} \xrightarrow[0°]{Ether} \begin{bmatrix} SLi \\ SLi \end{bmatrix} \xrightarrow[60\%]{TMSCl} \begin{bmatrix} STMS \\ STMS \end{bmatrix} \quad (19)$$

Hooten and Allred [66] were the first to report a synthesis of thiosilane, 26. Methylthiomagnesium iodide was prepared by allowing methanethiol to react with methylmagnesium iodide. The magnesium thiolate was then allowed to react with chlorotrimethylsilane to produce the thiosilane, 26.

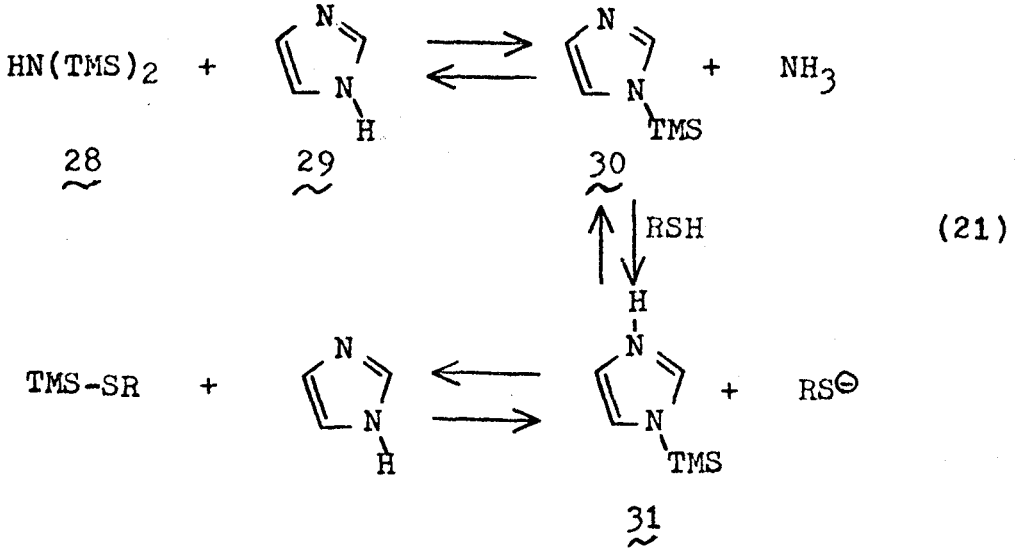
The thiosilane, 26, was also prepared by the $LiAlH_4$ reduction of dimethyldisulfide and subsequent reaction of the lithium aluminate, $(MeS)_4AlLi$, with chlorotrimethylsilane (eq. 20) [67].

Table II. Preparation of Thiosilanes.

Thiol	Silylation conditions	Thiosilane	Yield (%)	Refs.
EtSH	NaH, TMSCl	38	68	68
	n-BuLi, TMSCl	40	60	
	n-BuLi, TMSCl	39	40	
MeSH	n-BuLi, TMSCl	26	60	
MeSH	MeMgBr, TMSCl	26	33	66
	$LiAlH_4$, $(MeS)_2$, TMSCl	26	32	67
	TMS_2NH, imidazole	40	32	63
	TMS_2NH, imidazole	39	85	63

Although only thiosilane 26 has been prepared by this procedure, undoubtedly this method is general.

Glass [63] has developed another method for preparing thiosilanes. Hexamethyldisilazane, 28, and the corresponding thiol were reacted in the presence of a catalytic amount of imidazole, 29, (eq. 21).



(21)

Experiments suggest that imidazole is silylated by the silylamine, 28, and that this silylated imadazole then accepts a proton from the thiol [70]. The thiolate then attacks the protonated imidazole to form the thiosilane and regenerates the catalyst.In order to establish the intermediacy of 30, Glass has shown that when 30 and a thiol were

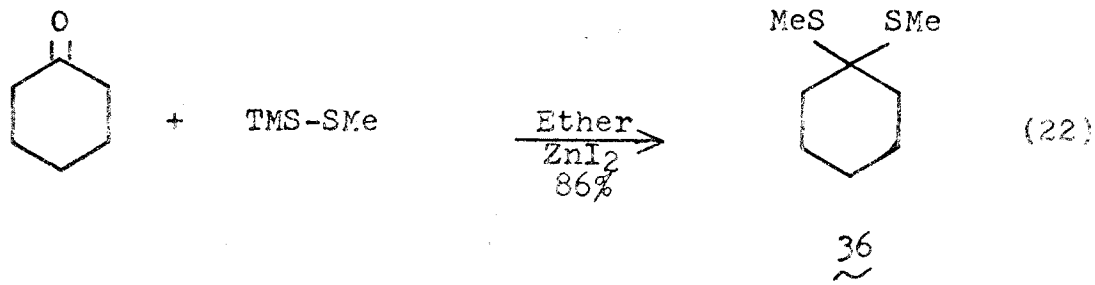
allowed to react, thiosilanes and imidazole were produced [71].

Thiosilane, 26, was prepared by the $LiAlH_4$ reduction of dimethyldisulfide, and by the reaction of chlorotrimethylsilane with the lithium or magnesium salts of methanethiol. However, the methylthiotrimethylsilane prepared via the reaction of methylthiomagnesium iodide with chlorotrimethylsilane, contained an impurity which catalyzed the thioketalization reaction. This impurity remained even after repeated distillations and although it was almost certainly another Lewis acid, the exact nature of this contaminant is still unknown.

Bis-1,2-trimethylthiosiloxyethane and bis-1,3-trimethylthiosiloxypropane were best prepared by the Glass procedure [63]. This method has the advantage of not forming inorganic salts and thus does not require a Schlenk filtration. Unfortunately, these reaction mixtures must be very carefully distilled prior to use in thioketalization reactions in order to remove all traces of amine 28. This amine inhibits the formation of thioketals and only silylhemithioketals are produced when thiosilanes are contaminated with amines. The sodium thiolates of 1,2-ethanedithiol and 1,3-propanedithiol could not be formed by reaction with NaH under the usual reaction conditions. To circumvent this problem, the thiolates were formed with n-butyllithium. This procedure, however, generates solid LiCl which must be removed by filtration before distillation.

SYNTHESIS OF THIOKETALS AND SILYLHEMITHIOKETALS

Ketones and aldehydes react with thiosilanes and a catalytic amount [4] of ZnI_2 to form thioketals and thioacetals (Table I). Cyclohexanone was converted to 1,1-dimethylthiocyclohexane, 36, by reaction with the thiosilane, 26, in a 92% yield (eq. 22) and other simple carbonyls react as efficiently. Ethylthiotrimethylsilane,

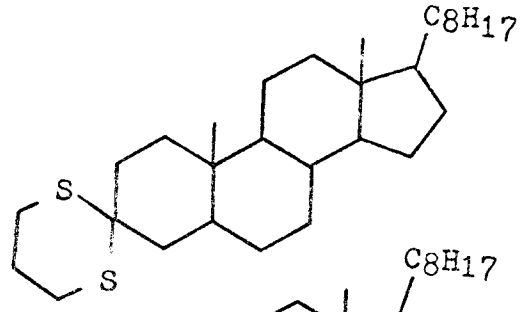
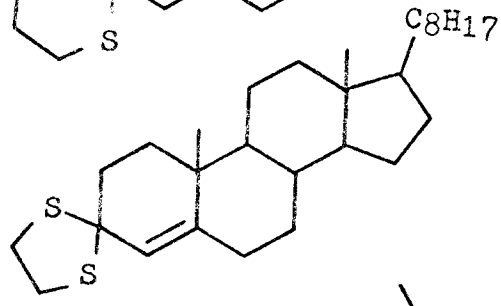
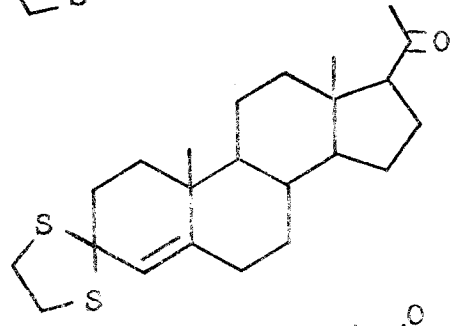
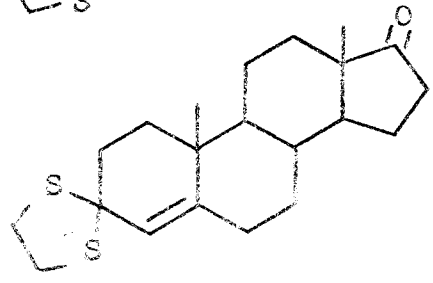


(22)

36

38, also reacts with carbonyls to produce thioketals and -acetals with efficienty equal to that of the thiosilane, 26 (Table I). Enones, such as cholestenone, fail to form a characterizable set of products when reacted with the thiosilane, 26. Presumably, elimination and olefin migration account for many of these products.

Table III. Thioketalization with Bifunctional Thiosilanes[a].

Carbonyl substrate	Product	Thiosilane[b]	Yield (%)
cholestenone		39	81
cholestenone		40	90
progesterone		40	93
androsteredione		40	94

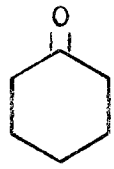
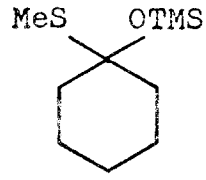
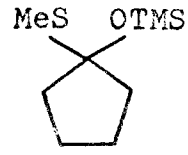
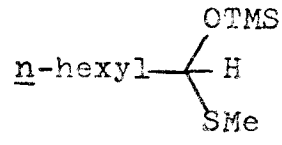
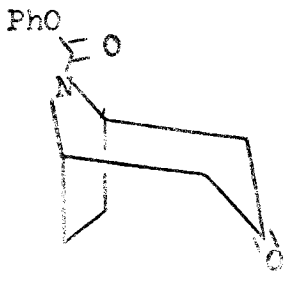
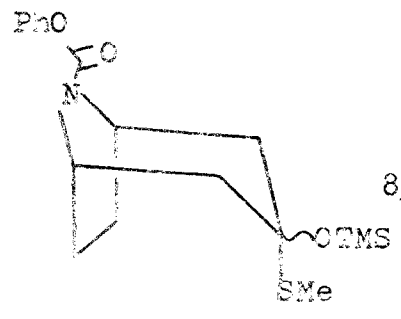
[a]All reactions were catalyzed with ZnI_2. [b]The reactions were performed with 1.1 equivalents of the thiosilane.

Thiosilane, 38, was allowed to react with 2-methyl-2-hydroxy-pentane-4-one and ZnI_2 in an effort to define the mildness of this thioketalization procedure. 2-Trimethylsiloxy-2-methyl-4,4-diethylthiopentane was isolated from the reaction mixture in a 92% yield. Although the rapid silylation of the alcohol probably keeps dehydration to a minimum, the absence of significant amounts of dehydration product demonstrates the mildness of the reaction conditions.

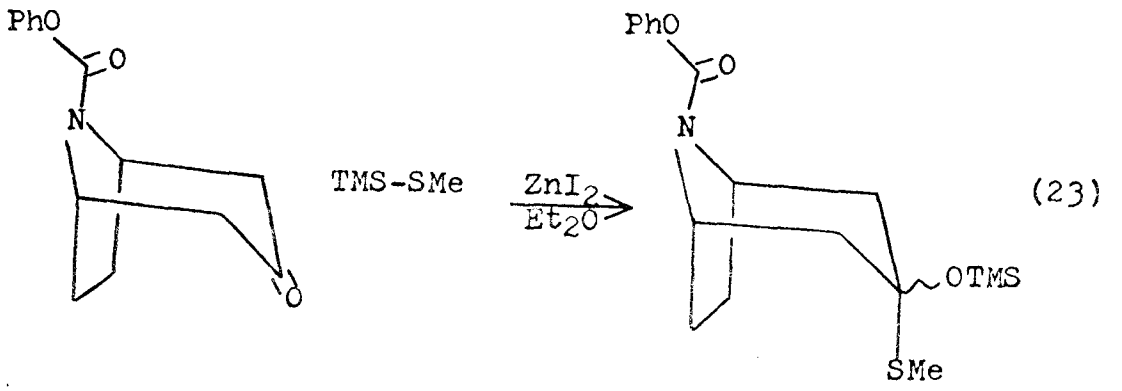
Silylhemithioketals and acetals can be prepared and isolated when ketones and aldehydes are reacted with ZnI_2 and a thiosilane which is contaminated with an amine (Table IV). This functional group has been investigated by Chan and Ong [24] in an effort to develop another reversed polarity carbonyl equivalent and although they were unsuccessful in generating the requisite anion, silylhemithioketals may still be used as carbonyl protecting groups in some applications.

8-Aza-8-carbophenoxy-bicyclo[3.2.1] octa-3-one, 42, has been converted to 8-aza-8-carbophenoxy-3-trimethylsiloxy-3-methylthiobicyclo[3.2.1]octane, 43, by allowing it to react with the thiosilane, 26, and ZnI_2 (eq. 23). Apparently the carbamate nitrogen deactivates the thioketalization process in the same manner that the amine, 28, does.

Table IV. Formation of Silylhemithioketals with Thiosilane 26[a,b].

carbonyl substrate	product	yield (%)	reaction time (hours)
		88	1.5
		72	1.0
n-hexyl-CHO		60	1.5
		85	24

[a]All reactions were catalyzed with ZnI_2. [b]The reactions were performed with 2 equivalents of 26.

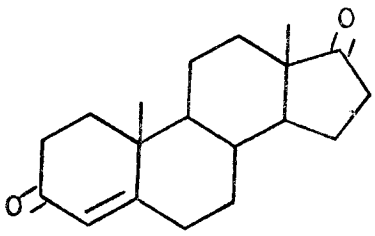


(23)

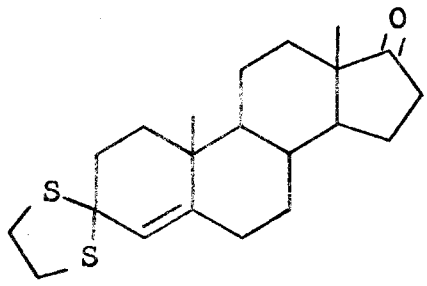
42 26 43

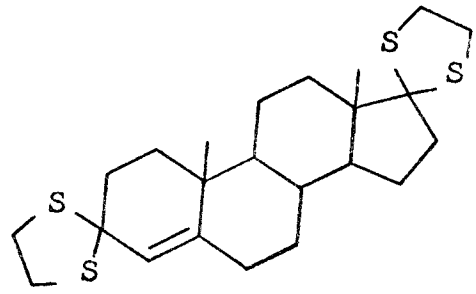
The thiosilane, 39, has been successfully used as a thioketalization reagent with unsaturated ketones. When the cholestenone was allowed to react with the thiosilane, 39, the 3-propylenethioketal of cholestenone, 49, was formed in an 81% yield. The thiosilane, 40, was also allowed to react with cholestenone, and the 3-ethylenethioketal, 50, was formed in a 90% yield.

Androsteredione was selectively thioketalized with the thiosilane, 40, to give the 3-ethylenethioketal of androsteredione, 44, as the major product and the bis-3,17-ethylenethioketal, 45, as the minor product (eq. 24).



$$\xrightarrow[ZnI_2]{RSCH_2CH_2SR} \qquad (24)$$

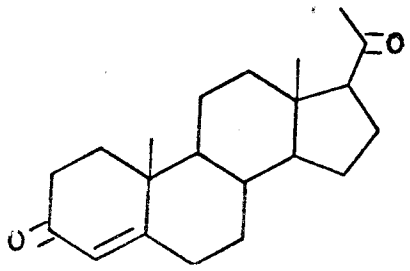




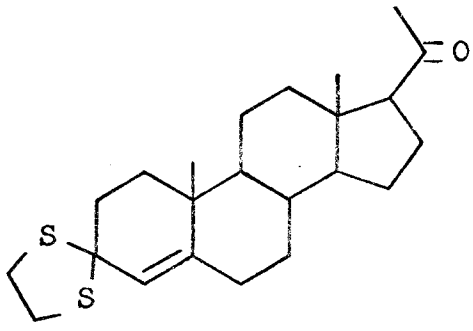
	44	45
R = TMS	91%	5%
R = H[42]	76%	10%

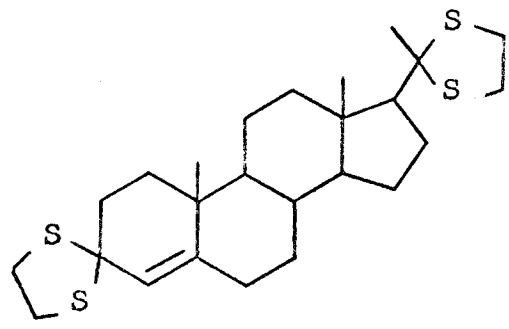
Progesterone was also selectively thioketalized with the thiosilane, 40, to give the 3-ethylenethioketal of progesterone, 46, as the major product and the bis-3,20-ethylenethioketal, 47, as the minor product (eq. 25). Both the overall yield and the positional selectivity of this thioketalization were superior to the normal thioketalization procedure employing ethanedithiol and $p\text{-}CH_3C_6H_4SO_3H$ [42].

Some steric hindrance at the β-position of enones may also be necessary for successful thioketalization. When cyclohexanone was allowed to react with the thiosilane, 40, a largely uncharacterized mixture of products was formed. The main component had an infrared



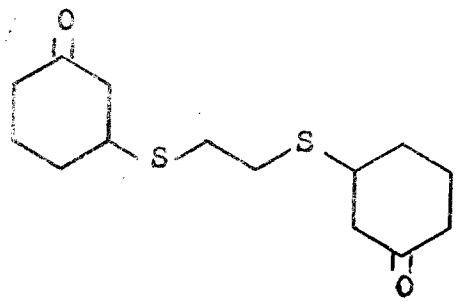
$$\xrightarrow[\text{acid}]{RSCH_2CH_2SR} \qquad (24)$$





	46	47
R = H[42]	35%	2%
R = TMS	94%	4%

spectrum and a proton magnetic resonance spectrum consistent with bis 1,2(3-oxocyclohexylthionyl) ethane, 48.



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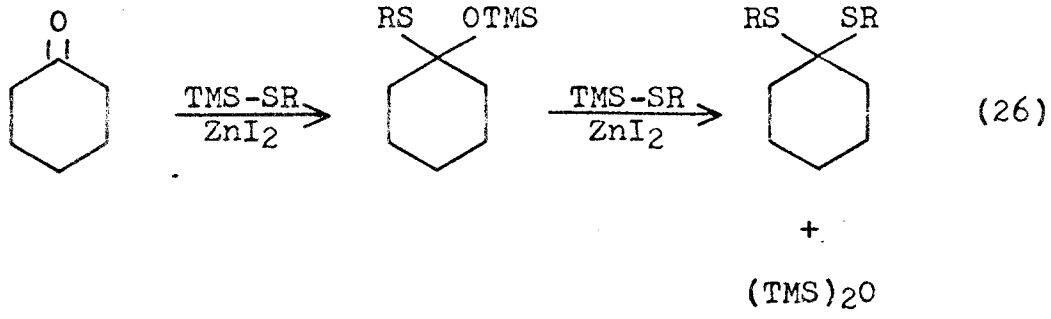
MECHANISTIC CONSIDERATIONS

The thioketalization reaction presumably proceeds through an O-trimethylsilylalkylthiohemiketal intermediate as illustrated with cyclohexanone (eq. 26). The first step of this reaction is analogous

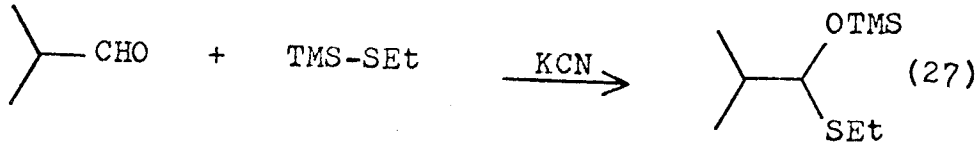


(26)

to the insertion reactions of carbonyl compounds with other organometallic reagents [64]. Experiments indicate that the thiosilane insertion process is Lewis acid assisted because no reaction occured when cyclohexanone and the thiosilane, 26, were mixed and the intermediate, 1-methylthio-1-trimethylsiloxycyclohexane, 33, also did not react with the thiosilane, 26, without added ZnI_2.

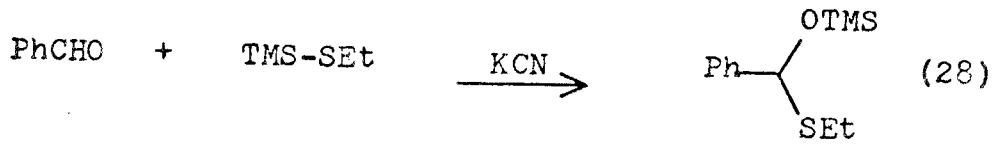
Anionic catalysts, such as potassium cyanide-18-crown-6-complex, have been used to form the intermediate silylhemithioacetals from aldehydes but anionic catalysts will not convert the intermediate silylhemithioketals and -acetals to thioketals and thioacetals. These anionic catalysts do not effect these reactions with ketones. Employing KCN as the catalyst, thiosilane, 38, was allowed to react with isobutyraldehyde to form 1-ethylthio-1-trimethylsiloxy-2-

methylpropane, 34, (eq. 27). Benzaldehyde was allowed to react with thiosilane, 38, to form α-trimethylsiloxy-α-ethylthiotoluene, 35 (eq. 28).



(27)

34



(28)

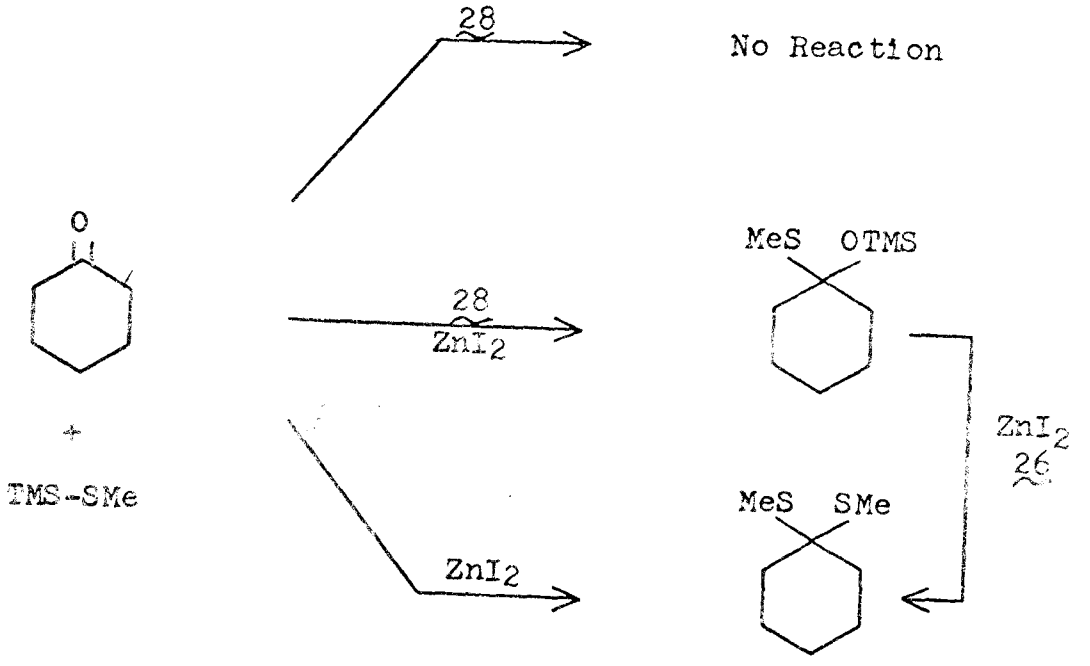
35

Both the amine, 28, and imidazole inhibit the normal thioketalization process and even with added ZnI_2, only silylhemithioketals are formed. Variations in the Lewis acid, even acids as strong as $AlCl_3$ and HCl, cause no change in the product. Heating these reaction mixtures caused only extensive elimination.

During the course of the thioketalization of cyclohexanone, gas chromatographic analysis revealed the rapid disappearance of the ketone and formation of a new product at longer retention time.

The new product had a retention time identical to that of the proposed intermediate, 1-methylthio-1-trimethylsiloxycyclohexane, 32. At longer reaction times this intermediate disappeared and was replaced by the product thioketal, 36. Furthermore, if the reaction was performed in the presence of the amine, 28, a substance known to inhibit the second step, the same intermediate peak appeared and isolation and structure proof verified that this intermediate was the hemithioketal, 32. The intermediate was then treated with the thiosilane, 26, and ZnI_2 and converted to the thioketal, 36 (Scheme I). Thus the proposed intermediate, 32, has been observed during the reaction, isolated from the reaction mixture and when resubmitted to the reaction conditions, was converted to the product thioketal, 36.

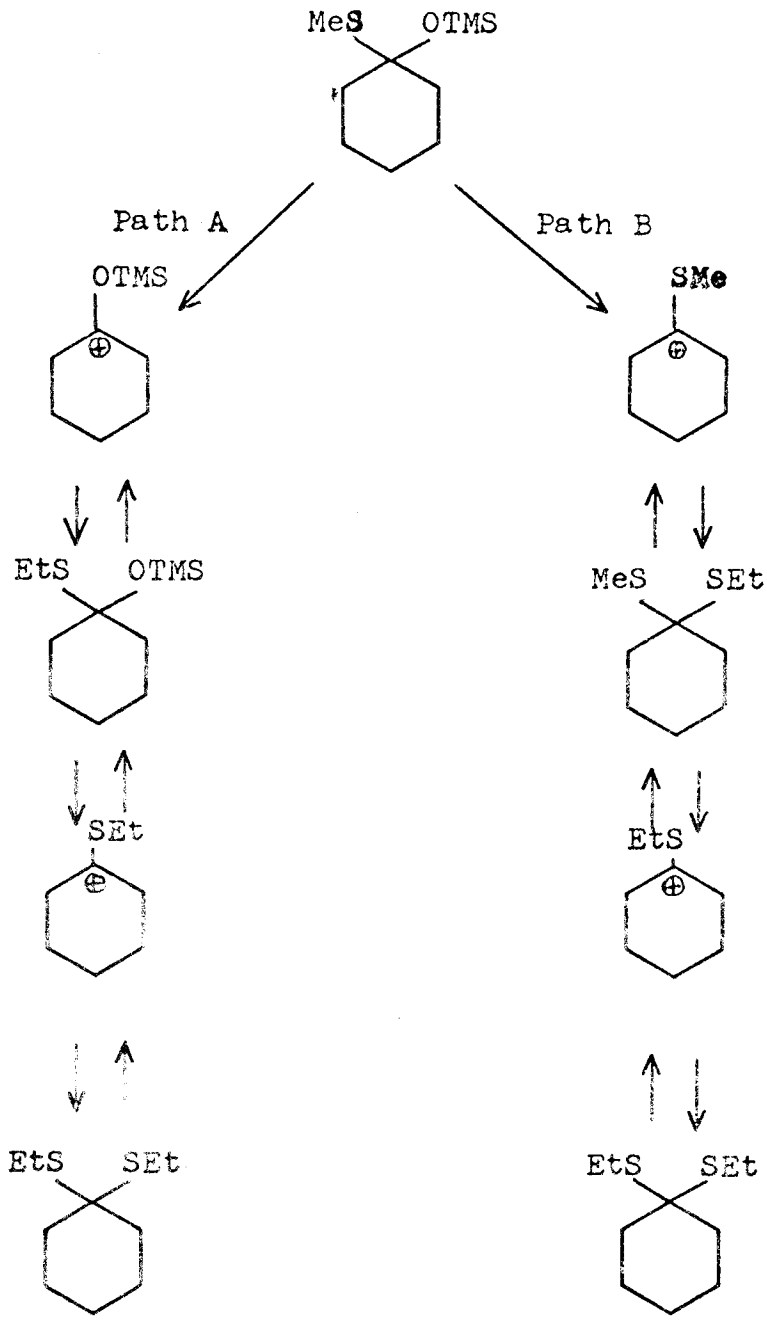
Scheme I



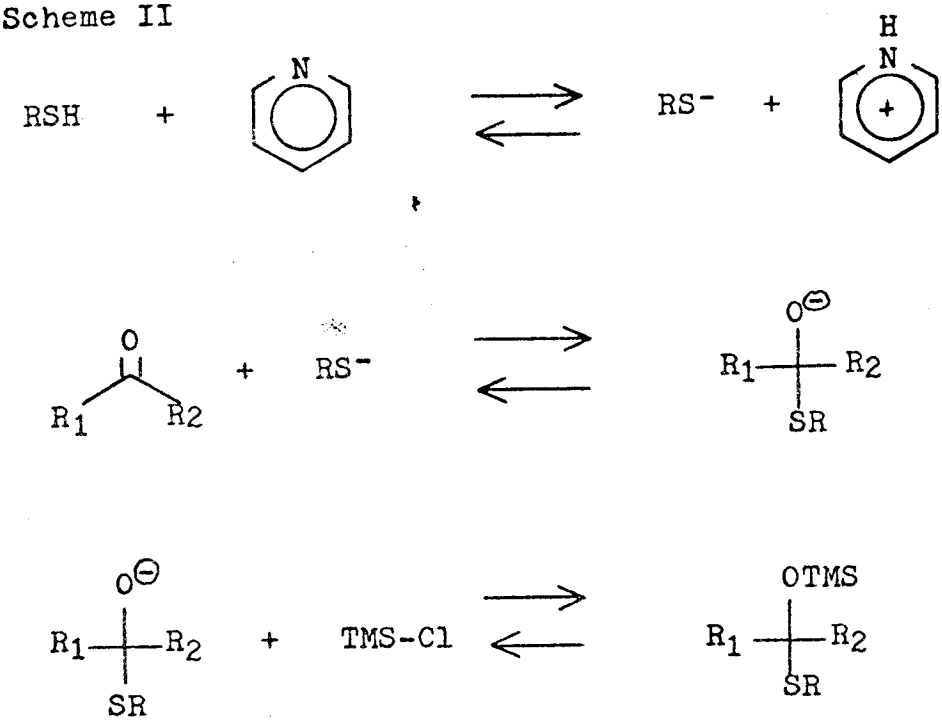
It is known that oxygen stabilized carbonium ions are more stable than sulfur stabilized carbonium ions [29]. From this data, it was predicted that if hemithioketal, 32, was allowed to react with hemiketal , 32, and ZnI_2, the reaction would follow path A of Scheme II and only thiosilane, 38, would be formed. If, however, path B was faster than or as fast as path A of Scheme II, then thiosilane 38 and 1-methylthio-1-ethylthiocyclohexane, 37, would be formed as a mixture. Unfortunately, the product thiosilanes interconvert under the reaction condition and lacking kinetic data, no conclusions can be made.

A recent report by Chan and Ong [24] described the formation of O-trimethylsilylmethylthiohemiketals and -acetals by the reaction of a thiol, pyridine, chlorotrimethylsilane and a ketone or aldehyde. They noted that if pyridine was omitted from the reaction mixture, only thioketals and -acetals were obtained. The mechanism proposed for the formation of thiohemiketals is shown in Scheme II. In light of the results presented here, it is proposed that trimethylalkylsilanes are formed in situ and that these thiosilanes react with ketones and aldehydes to produce thiohemiketals and -acetals which in the absence of pyridine and catalyzed by the HCl produced, react further to form thioketals and -acetals. Although no comparative rate studies of the thiol addition to carbonyl groups and chlorosilanes are presently known, it is not unreasonable to

Scheme II


MeS
OTMS
Path A
Path B
OTMS
SMe
EtS
OTMS
MeS
SEt
SEt
EtS
EtS
SEt
EtS
SEt

Scheme II



assume that the thiolates attack the silicon atom (a very electrophilic atom) faster than they attack the carbonyl carbon atom.

CONCLUSIONS

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When thiosilanes are allowed to react with aldehydes or ketones and a trace of ZnI_2, thioketals and thioacetals are formed in excellent yields. These conditions are the mildest and most efficient available. In addition, several steroidal diketones were thioketalized with yields and selectivity superior to that previously reported. This thioketalization procedure, however, requires the additional preparation of the thiosilane and the thiosilane must be carefully purified before use. In addition, ketones with amide or amine functionalities cannot be thioketalized by this procedure because only silylhemithioketals are produced.

The overall thioketalization process proceeds through silylhemithioketal intermediates which can be detected and isolated from the reaction mixture. Finally, the silylhemithioketals can be submitted to the thioketalization reaction conditions and be converted to thioketals.

EXPERIMENTAL

General. Infrared spectra were recorded on a Beckman IR-4210. PMR spectra were recorded on a Varian T-60 or A-60-A spectrometer and the chemical shifts are relative to either tetramethylsilane or methylene chloride (317 Hz). Gas chromatographic analysis were performed on a Varian Aerograph Series 1400 gas chromatograph using a 2 meter, stainless-steel column packed with SE-30 on Chromasorb W. Melting points were taken on a Büchi model SMP-20 melting point apparatus and are uncorrected. All solvents were dried by the procedures described in Perrin, Armarege and Perrin[68].

General Thioketalization Procedure. To a dry, nitrogen-purged, 25-ml, round-bottom flask was added ca. 0.01 g (0.03 mmol) of anhydrous zinc iodide, 5.0 ml of anhydrous ether, and 10 mmol of ketone or aldehyde. To this solution was added 22 mmol of the appropriate thiosilane, RS-TMS, via syringe over a 2 minute period. After stirring at ambient temperature (25°) for 12-24 hours, the reaction was quenched with water and extracted with ether. The etheral extract was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The resulting thioketal was then purified by chromatography on 50 g of alumina (Activity III) eluting with hexane.

1,1-Dimethylthioheptane. The general thioketalization procedure (1.40 ml, 10 mmol, heptanal; 3.20 ml, 22 mmol, 26) gave, after chromatography, 1.78 g (93.0%) of the product; ir (neat) 2960-2865, 1465, 1435, 955 cm^{-1}; nmr (CCl_4) δ 3.60 (t, 1, J=7.0 Hz, SCH), 2.10 (s, 6, SCH_3), 1.30 (m, 13, CH_2), 0.95 (t, 3, CH_3) ppm.

Anal. Calcd for $C_9H_{20}S_2$: C, 56.19; H, 10.48. Found: C, 56.11; H, 10.58.

1,1-Diethylthioheptane. The general thioketalization procedure (1.40 ml, 10 mmol, heptanal; 3.60 ml, 22 mmol, 38) gave, after chromatography and molecular distillation (90°/0.02 mm Hg), 2.03 g (92.0%) of the product; ir (neat) 2960-2860, 1450, 1260 cm^{-1}; nmr (CCl_4) δ 3.75 (t, 1, J=7.0 Hz,CH), 2.68 (q, 4, J=7.0 Hz, SCH_2), 1.40 (m, 13, CH_2), 1.30 (t, 6, J = 7.0 Hz, CH_3) ppm.

Anal. Calcd for $C_{11}H_{24}S_2$: C, 59.93; H, 10.97. Found: C, 59.78; H, 10.85.

2-Heptyl-1,3-dithiane. The general thioketalization procedure (1.40 ml, 10 mmol, heptanal; 3.01 ml, 11 mmol, 39) gave, after chromatography, 0.31 g (75.0%) of the product; ir (neat) 2960-2862, 1462, 1418, 1274,907 cm^{-1}; nmr (CCl_4) δ 4.00 (t, 1, methyne), 2.82 (m, 4, SCH_2), 2.00 (m, 2, SCH_2CH_3), 1.50 (m, 10, CH_2), 0.95 (t, 3, CH_3) ppm.

Anal. Calcd for $C_{10}H_{20}S_2$: C, 58.76; H, 9.86. Found: C, 58.85; H, 9.79.

1,1-Dimethylthiocyclopentane. The general thioketalization procedure (0.89 ml, 10 mmol, cyclopentanone; 3.20 ml, 22 mmol, 26) gave, after chromatography, 1.52 g (93.0%) of the product; ir(neat) 2960-2870, 1435, 1418 cm^{-1}; nmr (CCl_4) δ 2.05 (s, 6, SCH_3), 1.90 (m, 8, CH_2) ppm.

Anal. Calcd for $C_7H_{14}S_2$: C, 51.80; H, 8.69. Found: C, 52.03; H, 8.68.

1,1-Dimethylthiocyclohexane. The general thioketalization procedure (1.04 ml, 10 mmol, cyclohexanone; 3.20 ml, 22 mmol, 26) gave, after chromatography, 1.62 g (92.0%) of the product; ir (neat) 2978-2860, 1445, 1010, 755 cm^{-1}; nmr (CCl_4) δ 2.05 (s, 6, SCH_3), 1.70 (m, 10, CH_2) ppm.

Anal. Calcd for $C_8H_{16}S_2$: C, 54.49; H, 9.15. Found: C, 54.76; H, 8.98.

1,1-Diethylthiocyclohexane. The general thioketalization procedure (1.04 ml, 10 mmol, cyclohexanone; 3.60 ml, 22 mmol, 38) gave, after chromatography, 2.00 g (98.0%) of the product; ir (neat) 2970-2860, 1442, 1260,1257, 1005 cm^{-1}; nmr (CCl_4) δ 2.60 (q, 4, J=7.5 Hz, SCH_2), 1.75 (m, 10, CH_2), 1.27 (t, 6, J=7.5 Hz, CH_3) ppm.

Anal. Calcd for $C_{10}H_{20}S_2$: C, 58.75; H, 9.86. Found: C, 58.42; H, 9.57.

3,3-Diethylthiopentane. The general thioketalization procedure (1.05 ml, 10 mmol, 3-pentanone; 3.60 ml, 22 mmol, 38) gave, after chromatography, 1.74 g (91.0%) of the product; ir (neat) 2965-2870, 1450, 1370, 812 cm^{-1}; nmr (CCl_4) δ 2.60 (q, 4, J = 7.5 Hz, SCH_2), 1.65 (q, 4, J=8.0 Hz, CH_2), 1.25 (t, 6, J=7.5 Hz, CH_3), 1.00 (t, 6, J=8.0 Hz, CH_3) ppm.

Anal. Calcd for $C_9H_{20}S_2$: C, 56.19; H, 10.48. Found: C, 56.41; H, 10.28.

2,2-Diethyl-1.3-dithiane. The general thioketalization procedure (1.05 ml, 10 mmol, 3- pentanone; 3.01 ml, 11 mmol, 39) gave, after chromatography, 0.33 g (95.0%) of the product; ir (neat) 2970-2825, 1450, 1418, 903, 877 cm^{-1}; nmr (CCl_4) δ 2.75 (m, 4, SCH_2), 1.95 (m, 2,

CH_2), 1.90 (q, 4, CH_2), 0.95 (t, 6, CH_3) ppm; exact mass (75 eV) m/e calcd 176.069, observed 176.069.

α,α-Dimethylthiotoluene. The general thioketalization procedure (1.16 ml, 10 mmol, acetophenone; 3.20 ml, 22 mmol, 26) gave, after chromatography and molecular distillation (80°/0.07 mm Hg), 1.53 g (78.0 %) of the product; ir (neat) 3055, 2975-2820, 1593, 1442, 1250, 990, 860, 845, 695 cm^{-1}; nmr (CCl_4)δ 7.60 (m, 5, aryl-H), 2.10 (s, 6, SCH_3), 2.05 (s, 3, CH_3) ppm.

Anal. Calcd for $C_{10}H_{14}S_2$: C, 60.55; H, 7.11. Found: C, 60.64; H, 7.05.

α,α-Diethylthiotoluene. The general thioketalization procedure (1.16 ml, 10 mmol, acetophenone; 3.60 ml, 22 mmol, 38) gave, after chromatography, 2.11 g (93.0 %) of the product; ir (neat) 3055, 2965-2930, 1582, 1440, 695 cm^{-1}; nmr (CCl_4)δ 7.60 (m, 5, aryl-H), 2.62 (q, 4, J=7.5 Hz, SCH_2), 2.10 (s, 3, CH_3), 1.30 (t, 6, J=7.5 Hz, CH_3) ppm.

Anal. Calcd for $C_{12}H_{18}S_2$: C, 63.37; H, 8.01. Found: C, 63.41; H, 7.80.

1,1-Dimethylthio-2-methylpropane. The general thioketalization procedure (0.91 ml, 10 mmol, isobutyraldehyde; 3.20 ml, 22 mmol, 26) gave, after chromatography and molecular distillation (80°/0.04 mm Hg), 1.28 g (85.0 %) of the product; ir (neat) 2960-2870, 1460, 1435, 767 cm^{-1}; nmr (CCl_4)δ 3.42 (d, 1, J=6.0 Hz, SCH), 2.11 (s, 6, SCH_3), 1.97 (m, 1, CH), 1.15 (d, 6, J=6.0 Hz, CH_3) ppm.

Anal. Calcd for $C_6H_{14}S_2$: C, 47.94; H, 9.39. Found: C, 47.88; H, 9.42.

1,1-Diethylthio-2-methylpropane. The general thioketalization procedure (0.91 ml, 10 mmol, isobutyraldehyde; 3.60 ml, 22 mmol, 38) gave, after chromatography, 1.65 g (92.0 %) of the product; ir (neat) 2962-2930, 1450, 1260 cm^{-1}; nmr (CCl_4) δ 3.62 (d, 1, J=5.0 Hz, CH), 2.64 (q, 4, J=8.0 Hz, SCH_2), 2.05 (m, 1, CH), 1.28 (t, 6, J=8.0 Hz, $SCH_2\underline{CH_3}$), 1.10 (d, 6, J=5.0 Hz, CH_3) ppm.

Anal. Calcd for $C_8H_{18}S_2$: C, 53.87; H, 10.17. Found: C, 53.69; H, 9.87.

2-(1-Methyl)-ethyl-1,3-dithiane. The general thioketalization procedure (0.91 ml, 10 mmol, isobutyraldehyde; 3.01 ml, 11 mmol, 39) gave, after chromatography, 0.11 g (70.0 %) of the product; ir (neat) 2960-2820, 1452, 1415, 1272, 905 765 cm^{-1}; nmr (CCl_4) δ 3.60 (d, 1, RSCH), 2.80 (t, 4, SCH_2), 2.05 (m, 1, CH), 2.05 (p, 2, $SCH_2\underline{CH_2}$), 1.15 (d, 6, CH_3) ppm; exact mass (75 eV) m/e calcd 162.054, observed 162.055.

2,2-Diethylthio-4-methyl-4-trimethylsiloxypentane. The general thioketalization procedure (1.16 g, 10 mmol, 2-hydroxy-2-methylpentan-4-one; 5.40 ml, 33 mmol, 38) gave, after chromatography, 2.72 g (92.0 %) of the product; ir (neat) 2980, 2930, 2870, 1445, 1250, 1170, 1035, 858, 840, 750 cm^{-1}; nmr (CCl_4) δ 2.65 (q, 4, J=7.5 Hz, SCH_2), 2.05 (s, 2, CH_3), 1.70 (s, 3, CH_2), 1.45 (s, 6, CH_3), 1.30 (t, 6, J=7.5 Hz, $SCH_2\underline{CH_3}$), 0.20 (s, 9, $SiCH_3$) ppm; exact mass (75 eV) m/e calcd 204.101 for $C_9H_{18}S_2$, observed 204.101.

Reaction of cholestenone with thiosilane 39. The general thioketalization procedure (0.193g, 0.5 mmol, cholestenone; 0.31 ml, 1.1 mmol, 39) gave, after chromatography, 0.19 g (81.0 %) of the product;

ir ($CHCl_3$) 2940-2850, 1638, 1460, 1378, 1110, 908 cm^{-1}; nmr ($CDCl_3$) δ 5.45 (s, 1, =CH), 2.90 (m, 4, SCH_2), 2.20-1.10 (m, 30, alkyl), 1.13 (s, 3, CH_3), 0.95 (s, 3, CH_3), 0.85 (s, 3, CH_3), 0.72 (s, 6, CH_3); exact mass (75 eV) m/e calcd 474.335 for $C_{30}H_{50}S_2$, observed 474.338.

Reaction of cholestenone with thiosilane 40. The general thioketalization procedure (0.385 g, 1.0 mmol, cholestenone; 0.28 ml, 1.1 mmol, 40) gave, after recrystalization from acetone, 0.417 g (90.0 %) of the product;mp 110-112 , lit. value[42] 106-107 ; ir ($CHCl_3$) 2970-2850, 1635, 1460, 1433, 1377, 1370, 1272 cm^{-1}; nmr ($CDCl_3$) δ 5.40 (s, 1, CH), 3.30 (m, 4, SCH_2), 2.30-1.00 (m, 28, alkyl), 1.00 (s, 3, CH_3), 0.90 (s, 3, CH_3), 0.85 (s, 3, CH_3), 0.70 (s, 6, CH_3) ppm.

Reaction of androsteredione with thiosilane 40. The general thioketalization procedure (0.274 g, 1.0 mmol, androsteredione; 0.28 ml, 1.1 mmol, 40) substituting chloroform for ether, gave 0.408 g of crude product after 24 hours. Chromatography on silica gel (20 g) eluting with petroleum ether-benzene (1:2) gave 45 in a 5 % yield (mp 170-174 , lit. value ,mp 173-174.5)[42]; ir ($CHCl_3$) 2962-2850, 1635 (w) (C=C), 1433, 1130, 1105 cm^{-1}. Further elution with benzene-ethyl acetate (19:1) gave 44 in a 91 % yield (mp 170.5-171.5, lit. value, mp 173-174.5)[42]; ir (neat) 3000-2850, 1735 (s) (C=O), 1635 (w) (C=C), 1433, 1370, 1130,1105 cm^{-1}; nmr ($CDCl_3$) δ 5.55 (s, 1, =CH), 3.35 (m, 4, SCH_2), 2.50-1.20 (m, 19, alkyl), 1.08 (s, 3, CH_3), 0.90 (s, 3, CH_3) ppm.

Reaction of progesterone with thiosilane 40. The general thioketalization procedure (0.315 g, 1.0 mmol, progesterone; 0.28 ml, 1.1

mmol, 40), substituting chloroform for ether, gave 0.459 g of crude product after 24 hours. Chromatography on silica gel (20 g) eluting with petroleum ether-benzene (1:2) gave 47 in a 4 % yield (mp 175-179°, lit. value, mp 179-181.5°)[42]; ir ($CHCl_3$) 2970-2860, 1635 (w), 1130, 1105 cm^{-1}. Further elution with benzene-ethyl acetate (19:1) gave 46 in a 94 % yield (mp 177-181°, lit. value, mp 183-186°)[42]; ir ($CHCl_3$) 3000-2850, 1690 (s), 1130, 1105 cm^{-1}; nmr ($CDCl_3$) δ 5.50 (s, 1, =CH), 3.28 (m, 4, SCH_2), 2.10 (s, 3, $COCH_3$), 2.50-1.00 (m, 20, alkyl), 1.00 (s, 3, CH_3), 0.60 (s, 3, CH_3) ppm.

Preparation of 1-trimethylsiloxy-1-methylthiocyclohexane. To a 25-ml, round-bottom flask with a nitrogen atmosphere was added ca. 0.001 g of ZnI_2, 2.10 ml (1.96 g, 0.020 mole) of cyclohexanone and 3.20 ml (2.70 g, 0.022 mole) of the thiosilane, 26, which was contaminated with ca. 1 % of the amine, 28. After 1.5 hour, the reaction was quenched with water. This mixture was extracted with ether and the etheral extracts were washed with saturated NaCl solution and dried over anhydrous sodium sulfate. After filtration and solvent removal, the residue was filtered through alumina (Activity III) with hexane. Solvent removal allowed recovery of an 88 % yield of 1-methylthio-1-trimethylsiloxycyclohexane; ir (neat) 2950-2855, 1441, 1251, 1244, 1089, 1050, 835, 750 cm^{-1}; nmr (CCl_4) δ 2.10 (s, 3, SCH_3), 1.70 (m, 10, CH_2), 0.25 (s, 9, $SiCH_3$) ppm; exact mass (75 eV) m/e calcd 203.092 for $C_9H_{19}SiSO$, observed 203.092.

Preparation of 1-methylthio-1-trimethylsiloxyheptane. To a 25-ml, round-bottom flask with a nitrogen atmosphere was added ca. 0.001 g of ZnI_2, 2.80 ml (2.28 g, 0.020 mole) of heptanal and 3.20 ml (2.70 g,

0.022 mole) of the thiosilane, 26, which was contaminated to the extent of 1 % with the amine, 28. After 1.5 hours, the reaction mixture was quenched with water. This mixture was extracted with ether and the etheral extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After filtration and solvent removal, the residue was filtered through alumina (Activity III) with hexane. Solvent removal allowed the recovery of a 60 % yield of the product; ir (neat) 2960-2860, 1245, 840, 750 cm^{-1}; nmr (CCl_4) δ 4.70 (t, 1, CH), 2.05 (s, 3, SCH_3), 1.30 (m, 13, CH_2), 0.25 (s, 9, $SiCH_3$) ppm; exact mass (75 eV) m/e calcd 219.124 for $C_{10}H_{23}SiSO$, observed 219.123.

Preparation of 1-methylthio-1-trimethylsiloxycyclopentane. To a nitrogen-purged, 25 ml, round-bottom flask was added ca. 0.001g of ZnI_2, 1.78 ml (1.68 g, 0.020 mole) of cyclopentanone and 3.20 ml (2.70 g, 0.022 mole) of the thiosilane, 26, which was contaminated with the amine, 28. After 1.0 hour, the reaction was quenched with with water and this mixture was extracted with ether. The etheral extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After filtration and solvent removal, the residue was filtered through alumina (Activity III) with hexane. Solvent removal allowed recovery of a 72 % yield of the product; ir (neat) 2960-2870, 1245, 840, 753 cm^{-1}; nmr (CCl_4) δ 2.15 (s, 3, SCH_3), 1.90 (m, 8, CH_2), 0.25 (s, 9, $SiCH_3$) ppm; exact mass (75 eV) m/e calcd 189.077 for $C_8H_{17}SiSO$, observed 189.076.

Preparation of 8-aza-8-carbophenoxy-3-trimethylsiloxy-3-methylthio-bicyclo [3.2.1] octane. To a nitrogen purged, 50 ml, round-bottom

flask was added ca. 0.010 g of ZnI_2, 2.45 g (0.010 mole) of the ketone and 3.20 ml (2.64 g, 0.022 mole) of the thiosilane, 26. After 24 hours the reaction mixture was quenched with water and this mixture was extracted with ether. The etheral extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After solvent removal, the residue was filtered through alumina (Activity III) with benzene. The benzene was removed in vacuo to give an 85 % yield of the product; ir ($CHCl_3$) 3010-2930, 1705, 1410, 1330, 1250, 1095, 1055, 868. 842 cm^{-1}; nmr ($CDCl_3$) δ 7.85 (m, 5, aryl-H), 4.55 (s, broad,2,NCH), 2.50-2.10 (m, 8, alkyl), 2.25 (s, 3, SCH_3), 0.35 (s, 9, $SiCH_3$) ppm.

Anal. Calcd for $C_{18}H_{27}NO_3SiS$: C, 59.14; H, 7.45. Found: C, 59.13; H, 7.33.

Reaction of 1-methylthio-1-trimethylsiloxycyclohexane with thiosilane 38. To a nitrogen-purged, 10 ml, round-bottom flask was added 0.218 g (0.001 mole) of 32, ca. 0.0001 g of ZnI_2 and 0.485 ml (0.403 g, 0.003 mole) of 38. Gas chromatographic analysis after 8 hours revealed a mixture of 3 major constituents, thioketals 36, 37, 44. A high resolution mass spectra confirmed the existance of 44; exact mass (75 eV) m/e calcd 190.085 for $C_9H_{18}S_2$, observed 190.085.

Reaction of 1,1-dimethylthiocyclohexane with thiosilane 38. To a nitrogen-purged, 10 ml, round-bottom flask was added 0.176 g (0.001 mole) of 36, ca. 0.0001 g of ZnI_2 and 0.323 ml (0.268 g, 0.002 mole) of 38. Gas chromatographic analysis revealed a mixture; the 3 major constituents were found to be thioketals 36, 37, and 44.

Reaction of cyclohexanone with thiosilane, 26, and hexamethyldisilazane. To a nitrogen-purged, 5-ml flask was added ca. 0.0001 g of ZnI_2, 0.10 ml (0.098 g, 0.001 mole) of cyclohexanone, 1 μl of amine, 28, and 0.32 ml (0.264 g, 0.022 mole) of the thiosilane, 26. Gas chromatographic analysis after 0.75 hour indicated the majority of the product was 32 with only a trace of 36.

Reaction of silylhemithioketal, 32, with thiosilane, 26, in the absence of ZnI_2. To a nitrogen-purged, 5-ml flask was added 0.22g (0.001 mole) of the hemithioketal, 32, and 0.16 ml (0.132 g, 0.0011 mole) of the thiosilane, 26. Gas chromatographic analysis indicated no reaction.

Reaction of cyclohexanone with the thiosilane, 26, and imidazole. To a nitrogen-purged, 5-ml flask was added 0.001 g of ZnI_2, 0.10 ml (0.098 g, 0.001 mole) of cyclohexanone, ca. 0.001 g of imidazole and 0.32 ml (0.264 g, 0.0022 mole) of the thiosilane, 26. Gas chromatographic analysis indicated conversion to the hemithioketal, 32, and a trace of the thioketal, 36.

Reaction of the silylhemithioketal, 32, with the thiosilane, 26. To a nitrogen-purged, 5-ml flask was added ca. 0.001 g of ZnI_2, 0.22 g (0.001 mole) of the hemithioketal, 32, and 0.16 ml (0.132 g, 0.0011 mole) of the thiosilane, 26. Gas chromatographic analysis indicated the thioketal, 36, as the only product.

Reaction of cyclohexanone with the thiosilane, 26, in the absence of ZnI_2. To a nitrogen-purged, 5-ml flask was added 0.10 ml (0.098 g, 0.001 mole) of cyclohexanone and 0.32ml (0.264 g, 0.0022 mole) of the thiosilane, 26. Gas chromatographic analysis indicated no reaction.

Preparation of the thiosilane, 38. To a nitrogen-purged, 1-liter, 3-necked, round-bottom flask, equipped with a reflux condensor, a mechanical stirrer and an addition funnel was added 300 ml of anhydrous ether and 48.0 g (1.00 mole) of NaH (50 % dispersion in oil). Ethanethiol, 62.1 g (1.00 mole), was added dropwise over 6.0 hours. To the resulting slurry was added 125 ml (108.0 g, 1.05 mole) of chlorotrimethylsilane dropwise over a period of 1.5 hours. After stirring at ambient temperature for 12.0 hours, the mixture was filtered under nitrogen and distilled to give a 42 % yield of the thiosilane, 38; bp 128-130, lit. value[64], bp 127-131.

Preparation of the thiosilane, 39. Procedure 1. To a nitrogen-purged, 250-ml, 3-necked, round-bottom flask, equipped with a reflux condensor, a mechanical stirrer and an addition funnel was added 100 ml of anhydrous ether, 5.00 ml (5.40 g, 0.050 mole) of propanedithiol. While the reaction flask was cooled in an ice bath, 50.0 ml of n-butyllithium (2.0 M in hexane) was added dropwise over a period of 0.5 hour. After allowing the reaction mixture to warm to room temperature, 13.0 ml (10.9 g, 0.10 mole) of chlorotrimethylsilane was added over a period of 0.5 hour with efficient stirring. After the mixture had reacted at reflux temperature for 24 hours a filtration under nitrogen followed by a distillation (bp 75°/0.02 mm Hg) gave the thiosilane, 39, in a 40 % yield; nmr (CCl_4) δ 2.60 (t, 4, J=6.0 Hz, SCH_2), 2.92 (m, 2, CH_2), 0.38 (s, 9, $SiCH_3$) ppm; exact mass (75 eV) m/e calcd 252.086 for $C_9H_{24}Si_2S_2$, observed 252.086.

Preparation of the thiosilane, 39. Procedure 2. To a nitrogen-purged, 250-ml, round-bottom flask equipped with a reflux condensor

was added 0.30 g of imidazole, 79.0 ml (61.1 g, 0.38 mole) of hexamethyldisilazane and 10.0 ml (10.8 g, 0.10 mole) of 1,3-propanedithiol. The mixture was heated at reflux temperature for 24 hours. A careful distillation gave 21.6 g (85 %) of the thiosilane, 39.

Preparation of the thiosilane, 40. Procedure 1. To a nitrogen-purged, 100-ml, round-bottom flask equipped with a mechanical stirrer, a reflux condensor and an addition funnel was added 250 ml of anhydrous ether and 8.4 ml (9.42 g, 0.10 mole) of 1,2-ethanedithiol. While the reaction flask was cooled in an ice bath, 124 ml (0.20 mole) of n-butyllithium (1.61 M in hexane) was added dropwise over 0.5 hour. The reaction mixture was stirred efficiently during this addition. After the mixture was allowed to stand at room temperature for 3 hours, 26.0 ml (21.8 g, 0.20 mole) of chlorotrimethylsilane was added and the mixture was heated at reflux temperature for 12 hours. A filtration under nitrogen and a distillation (bp 80°/0.3 mm Hg, lit. value[63], bp 145-150°/40 mm Hg) gave the thiosilane, 40, in a 60 % yield; nmr (CCl_4) δ 2.60 (s, 4, SCH_2), 0.35 (s, 18, $SiCH_3$) ppm.

Preparation of the thiosilane, 40. Procedure 2. To a nitrogen-purged, 50-ml, round-bottom flask equipped with a reflux condensor was added 0.150 g of imidazole, 35.0 ml (27.0 g, 0.168 mole) of amine, 28, and 4.2 ml (4.7 g, 0.050 mole) of 1,2-ethanedithiol. This was allowed to react at reflux temperature for 24 hours and then carefully distilled to give a 32 % yield of the thiosilane, 40.

NOTES AND REFERENCES

NOTES AND REFERENCES

1. a) D. Seebach, M. Kolb, Chem. Ind., 7, 687 (1974);
   b) D. Seebach, M. Kolb, B. Grobel, Tetrahedron Lett., 317 (1974).
2. D. A. Evans, G. C. Andrews, Accts. Chem. Res., 7, 147 (1974).
3. a) J. E. Richman, J. L. Herrman, R. H. Schlessinger, Tetrahedron Lett., 3267 (1973); b) J. C. Herrman, J. E. Richman, R. H. Schlessinger, Tetrahedron Lett., 3275 (1973); c) G. Schill, P. R. Jones, Synthesis, 117 (1974); d) K. Ogura, G. Tsuchiheshi, Tetrahedron Lett., 3151 (1971);
   e) I. Hori, T. Hayashi, H. Midorikawa, Synthesis, 705 (1974);
   f) J. L. Herrman, J. E. Richman, P. J. Wepplo, R. H. Schlessinger, Tetrahedron Lett., 4707 (1973).
4. A catalytic amount in this report means ca. 1-2 molar %.
5. An earlier report from these labs claimed no acid catalysis was needed, however, this has subsequently been shown to be in error, also see ref. 67.
6. J. F. W. Keana,"Steroid Reactions"(Ed. C. Djerassi), Holden-Day, San Francisco, 1963.
7. H. J. E. Lowenthal, Tetrahedron, 6, 269 (1959).
8. J. F. W. McOmie, Adv. Org. Chem., 3. 191 (1963).

NOTES AND REFERENCES (Continued)

9. I. T. Harrison, S. Harrison, "Compendium of Organic Synthetic Methods," Vol. 1, J. Wiley and Sons, Inc., Chap. 4, 12, New York, 1971.

10. I. T. Harrison, S. Harrison, "Compendium of Organic Synthetic Methods," Vol. 2, J. Wiley and Sons, Inc., Chap. 4, 12, New York, 1974.

11. J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, New York, Chap. 9, (1973).

12. O. Isler, N. Lindlar, M. Montavan, R. Ruegg, G. Saucy, P. Zeller, Helv. Chim. Acta., 39, 2041 (1956).

13. J. E. McMurray, J. Amer. Chem. Soc., 90, 6821 (1968).

14. J. E. Cole, W. S. Johnson, P. A. Robins, J. Walker, J. Chem. Soc., 244 (1962).

15. M. Julia, S. Julia, M. Langlois, Bull. Soc. Chim. Fr., 1007 (1965).

16. N. H. Anderson, H. S. Uh, Synthetic Comm., 3, 125 (1973).

17. R. F. Fischer, C. W. Smith, J. Org. Chem., 28, 594 (1963).

18. K. J. Clark, G. I. Fray, R. H. Jaegar, R. Robinson, Tetrahedron, 6, 217 (1959).

19. N. B. Lorette, W. L. Howard, J. Org. Chem., 25, 521, 525 (1960).

20. J. J. Brown, R. H. Lenhard, S. Berstein, J. Amer. Chem. Soc., 86, 2183 (1964).

21. D. Hartley, J. Chem. Soc., 4722 (1962).

22. M. Nilsson, Acta. Chem. Scand., 12, 1830 (1958).

23. C. R. Engel, S. Rakhit, Can. J. Chem., 40, 2153 (1962).

NOTES AND REFERENCES (Continued)

24. T. H. Chan, B. S. Ong, Tetrahedron Lett., 319 (1976).

25. E. J. Corey, R. A. Ruden, J. Org. Chem., 38, 834 (1973).

26. D. P. Roelofsen, E. R. J. Wils, H. van Bekkum, Rec. Trav. Chim., 90, 1141 (1971).

27. The same equilibrium mixture was obtained by reacting a thiosilane and imidazole.

28. N. B. Lorette, W. C. Howard, J. H. Brown, J. Org. Chem., 24, 1731 (1959).

29. H. Bohme, K. Sell, Chem. Ber., 81, 123 (1948).

30. G. J. Rosenkranz, J. Pataki, C. Djerassi, J. Org. Chem., 17, 187 (1974).

31. J. Hebart, D. Gravel, Can. J. Chem., 52, 187 (1974).

32. E. J. Corey, R. A. Ruden, J. Org. Chem., 38, 834 (1973).

33. For a similar transformation see J. L. Isidor, R. M. Carlson, J. Org. Chem., 38, 554 (1973).

34. J. Romo, G. Rosenkranz, C. Djerassi, J. Amer. Chem. Soc., 73, 4961 (1951).

35. R. H. Mazar, E. A. Brown, J. Amer. Chem. Soc., 77, 6670 (1955).

36. P. J. Barrey, B. M. Craig, Can. J. Chem., 33, 716 (1955).

37. H. Hauptman, J. Amer. Chem. Soc., 69, 562 (1947).

38. J. W. Ralls, R. M. Dodson, B. Riegel, J. Amer. Chem. Soc., 71, 3320 (1949).

39. R. T. Blickenstaff, E. L. Foster, J. Org. Chem., 26, 5029 (1961).

40. H. Zinner, H. Brandner, G. Rembarz, Chem. Ber., 89, 800, 1507 (1956).

NOTES AND REFERENCES (Continued)

41. H. Zinner, G. Rembarz, H. Linke, G. Ulbricht, Chem. Ber., 90, 1761 (1957).

42. J. W. Ralls, B. Riegel, J. Amer. Chem. Soc., 76, 4479 (1954).

43. L. F. Fieser, J. Amer. Chem. Soc., 76, 1945 (1954).

44. 1-Trimethylsilylimidazole has been shown to be more basic than hexamethyldisilazane.

45. F. Bessette, J. Brault, J. M. LaLancette, Can. J. Chem., 43, 307 (1965).

46. J. M. LaLancette, A. Lachance, Can. J. Chem., 47, 859 (1969).

47. E. J. Corey, R. B. Mitra, J. Amer. Chem. Soc., 84, 2938 (1962).

48. D. Seebach, B. W. Erickson, G. Singh, J. Org. Chem., 34, 4303 (1966).

49. P. R. Heaton, J. M. Midgley, W. B. Whalley, Chem. Commun., 750 (1971).

50. W. D. Kingsbury, C. R. Johnson, Chem. Commun., 365 (1969).

51. E. J. Corey, B. W. Erickson, J. Org. Chem., 36, 3553 (1971).

52. E. L. Eliel, A. A. Hartmann, J. Org. Chem., 37, 505 (1972).

53. D. W. Emerson, H. Wynberg, Tetrahedron Lett., 3445 (1971).

54. W. F. J. Huurdeman, H. Wynberg, D. W. Emerson, Tetrahedron Lett., 3449 (1971).

55. K. Ogura, G. Tsuchihashi, Tetrahedron Lett., 3151 (1971).

56. R. Kuhn, W. Baschang-Bister, Justus Liebigs Ann. Chem., 641, 160 (1961).

NOTES AND REFERENCES (Continued)

57. D. Gravel, C. Vaziri, S. Rahal, Chem. Commun., 1323 (1972).

58. T. Oishi, K. Kamemoto, Y. Ban, Tetrahedron Lett., 1085 (1972).

59. C. Djerassi, L. Miramontes, G. Rosenkranz, F. Sonderheimer, J. Amer. Chem. Soc., 76, 4092 (1954).

60. W. Lidy, W. Sundermeyer, Chem. Ber., 106, 587 (1973).

61. D. A. Evans, L. K. Truesdale, G. L. Carroll, Chem. Commun., 55 (1973).

62. D. A. Evans, J. M. Hoffman, L. K. Truesdale, J. Amer. Chem. Soc., 95, 5822 (1973).

63. R. S. Glass, J. Orgmet. Chem., 61, 83 (1973).

64. L. K. Truesdale, Ph. D. Thesis, University of California, Los Angelos, California, 1974.

65. S. H. Langer, S. Connell, I. Wender, J. Org. Chem., 23, 50 (1958).

66. K. A. Hooton, R. L. Allred, J. Inorg. Chem., 4, 671 (1965).

67. D. A. Evans, K. G. Grimm, L. K. Truesdale, J. Amer. Chem. Soc., 97, 3230 (1975).

68. D. D. Perrin, W. L. F. Armarego, D. R. Perrin, "Purification of Laboratory Chemicals," Pergamon Press, New York, 1966.