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THE APPLICATION OF HETEROCYCLES TO THE SYNTHESIS OF CARBONYL COMPOUNDS

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The role of heterocyclic compounds in the synthesis of substituted aldehydes and ketones is reviewed. Particular note is made of the charge polarization of the masked carbonyl function and the sites of alkylation available with each heterocycle are considered. A total of eleven heterocycles are discussed.

Introduction

This review surveys some of the applications of various heterocyclic compounds as aids to the synthesis of molecules containing carbonyl functionality. These heterocycles are 'masked' carbonyls which can serve a dual purpose; protection of the carbonyl and/or modification of its chemical character. The latter result is generally due to a differing charge distribution in the heterocycle from that in the parent carbonyl compound.

Because of the scope of this topic, it was necessary to limit arbitrarily the areas which would be treated. The heterocycles discussed are those in which:

1) a carbonyl group results upon cleavage of the heterocycle (demasking);
2) this carbonyl is an aldehyde or ketone;
3) the heterocycle is such that there is the potential for generation of either a positive or negative charge at the carbonyl carbon atom;
4) alkylation of the heterocycle must be possible (i.e. it does not act solely as a protecting group)[1].

(1) Carbonyl transpositions are not included, as no formal alkylation occurs in these processes.

The heterocycles in question thus fit into two broad categories. One class is that in which the 'carbonyl' carbon[2] is electrophilic (i.e. normal carbonyl polarity) and the other includes heterocycles in which the opposite polarization is developed. Because of this method of organization, and their analogous behaviour to 1,3-dithianes, thioacetal monosulphoxides were included in the latter grouping, although they are not strictly speaking, heteroCYCLES. Also, heterocycles which can behave in either fashion, such as furan derivatives, were not considered, as this characteristic is not suited to the format of this paper.

Normal Polarization

Reverse Polarization

Within each of the two main divisions noted above, the further distinction as to whether alkylation occurs at the masked carbonyl, α to this position, or β to it was made.

Notwithstanding the limitations placed on the topic of this review, it was not possible to include all classes of heterocycles which met the criteria applied. Hopefully, the ones chosen illustrate the range of synthetic possibilities and give a balanced view of their uses.

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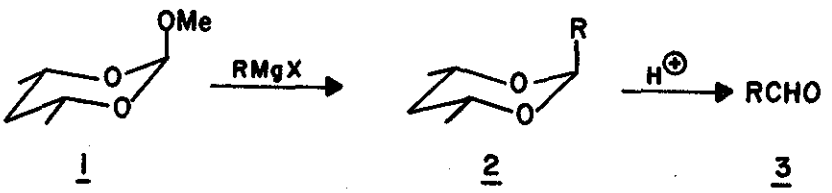
[2] Throughout this review, "'carbonyl' carbon" is used to denote the carbon of the heterocycle which becomes the carbon of the carbonyl upon deblocking.

Heterocycles Yielding Normal Carbonyl Charge Polarization

1) 1,3-Dioxanes

Treatment of 2-methoxy-1,3-dioxanes 1, in which the methoxy substituent has the axial configuration, with a Grignard reagent afforded[1] a 1,3-dioxane derivative, 2. This process is equivalent to the formylation of a Grignard, as acidic hydrolysis of 2 gives the aldehyde 3. It was noted that if the methoxy group was equatorially



1 2 3

oriented, it was not displaced by the Grignard reagent.

1 was prepared from the corresponding diol and trimethyl orthoformate. 90 to 95% of the product possessed the axial 2-substituent.

Table 1

Yields of 2-alkyldioxanes from Grignard treatment of 1

RMgX	% 2
Me-	70%
Et-	75
i-Pr-	63
ø-	95
p-F-ø-	94
p-Br-ø-	55
p-CF_3-ø-	89

2) Quinazolines

Grignard formylation is also feasible via the quinazoline methiodide 4[2], which was prepared by heating p-toluidine, formalin solution, and formic acid, followed by quaternization with methyl iodide. Both aliphatic and aryl Grignard reagents added to 4, generating 5, which was converted to the aldehyde by acidic hydrolysis. Yields for the sequence from 4 to 6 generally ranged between 70 and 95% (see Table 2).

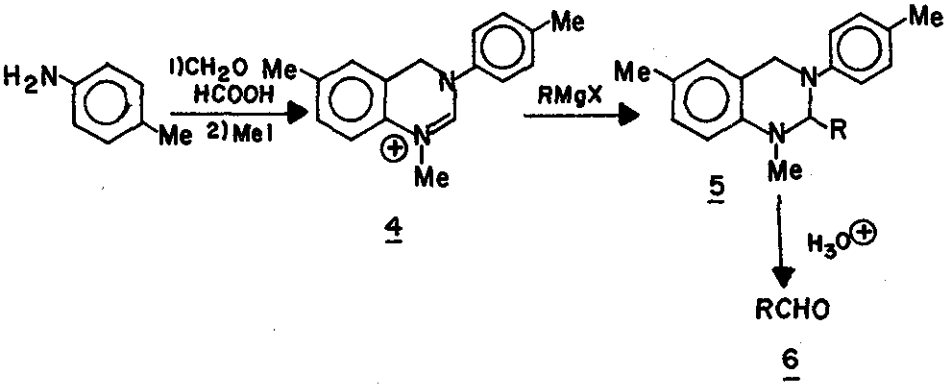


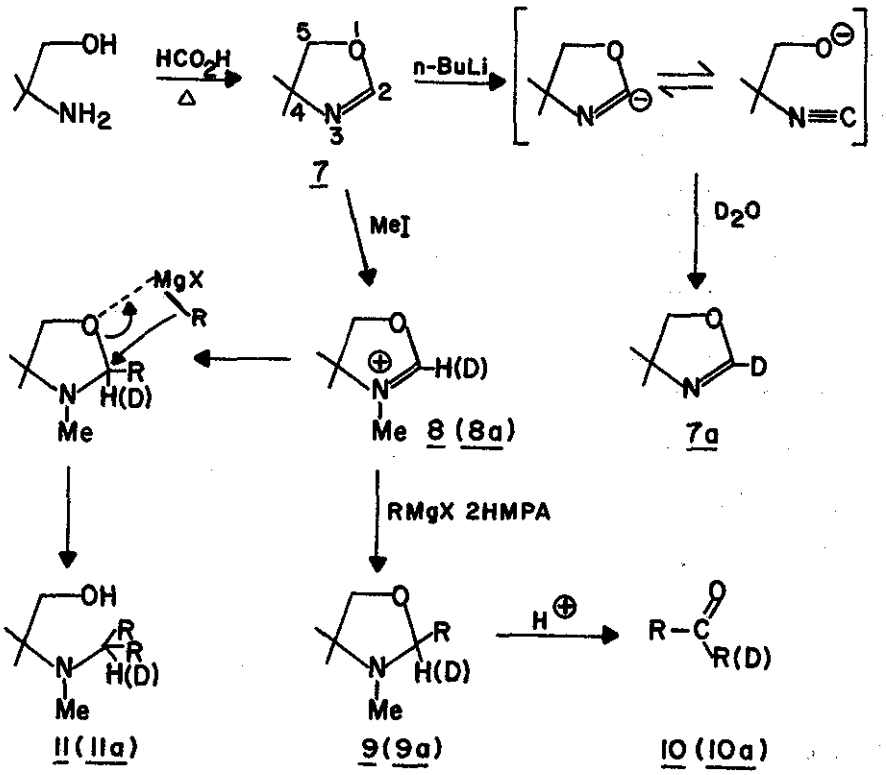
Table 2

Aldehydes prepared via the quinazoline methiodide 4

RMgX	Product (isolated as DNP derivative)	Yield
CH_3MgI	CH_3CHO	78%
n-C_4H_9MgBr	n-C_4H_9CHO	87
ϕCH_2MgCl	ϕCH_2CHO	74
n-$C_{12}H_{25}MgBr$	n-$C_{12}H_{25}CHO$	73
Et(Me)CHMgBr	Et(Me)CHCHO	34
$Me_2CHMgBr$	Me_2CHCHO	45
$\phi MgBr$	ϕCHO	95
p-CH_3O-$\phi MgBr$	p-CH_3O-ϕCHO	80
2,5-$(CH_3O)_2$-$\phi MgBr$	2,5-$(CH_3O)_2$-ϕCHO	34

3) 2-Oxazolines[3]

A third heterocycle which allows Grignard formylation is the substituted 2-oxazoline, 7[4], which can be prepared[5] by heating 2-amino-2-methylpropanol with formic acid. Treatment of 7 with n-butyllithium causes abstraction of



the C-2 proton and quenching with D_2O gives the deuterated analogue 7a. The methiodide salt of 7 or 7a is the substrate susceptible to the Grignard reagent. The latter must be complexed with two equivalents of hexamethylphosphoramide (HMPA), or the amino alcohol 11 or 11a results. It is believed that the oxazolidine, 9 or 9a, is initially formed and it then complexes with the Grignard reagent as shown above.

The aldehyde is liberated from 9 or 9a by hydrolysis with oxalic acid.

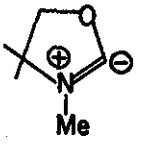
Thus this method provides a simple synthesis of aldehydes and C-1 deuterated aldehydes. However, it is limited to Grignard reagents with an sp^2 or sp hybridized carbanion. The base strength of aliphatic Grignards in HMPA is

Table 3

Yields of aldehydes produced from the reaction of 2-oxazolines and Grignard reagents

RMgX	% 10 (10a)
ϕCH_2-	87
ϕCH=CH-	64
ϕC≡C-	51
o-(MeO)-ϕ-	90 (70)

such that there is considerable proton abstraction from 8 in competition with addition. The ylides 12 and 13 are generated in these instances.



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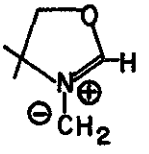

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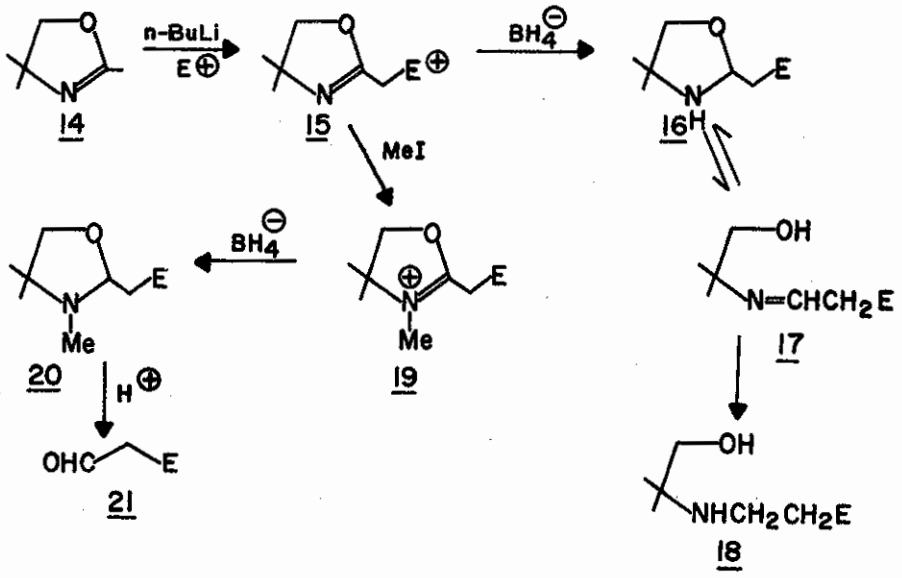
All the examples of heterocycles so far cited have involved alkylation at the masked carbonyl carbon. 2-Substituted oxazolines, which are also prepared from 2-amino-2-methylpropanol and a carboxylic acid, can be alkylated α to this site as well[6-8]. Aliphatic reagents may be used in this variation.

2,4,4-Trimethyl-2-oxazoline, 14, can be alkylated using n-butyllithium and a variety of electrophiles[6]. Suitable ones include alkyl halides, epoxides, and carbonyl compounds. If 15 is reduced directly with borohydride, the amino alcohol 18 results. This is due to the equilibrium of the oxazolidine 16 with the acyclic species 17, which is further reduced. However, the methiodide



19 is reduced to the saturated cyclic derivative 20, acid hydrolysis of which yields the corresponding aldehyde.

2-Substituted oxazolines may also be converted to unsymmetrical ketones[7]. When 22 is treated with two equivalents of an alkyllithium reagent at -78°, the hydrogen α to the ring is removed by the first equivalent of base. As

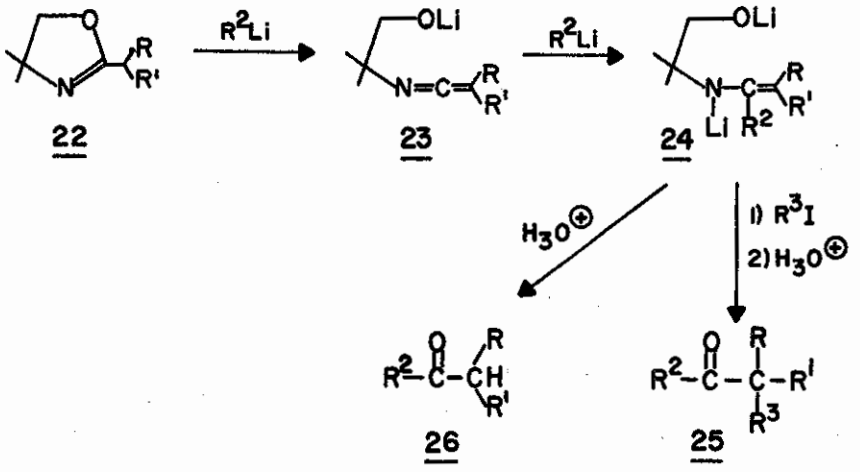


Table 4

Ketones (25,26) from the alkylation of 2-substituted oxazolines

R	R^1	R^2	R^3	Yield (25 or 26)
Me	Me	Et		89%
Me	Me	i-Pr		69
Me	Et	Et		76
Et	Et	Et		91
i-Pr	Me	Et		83
i-Pr	Et	Et		85
i-Pr	Et	Et		65
i-Pr	i-Pr	i-Pr		83
t-Bu	H	t-Bu		74
t-Bu	Me	t-Bu		71
t-Bu	Et	t-Bu		29
t-Bu	i-Pr	t-Bu		37
t-Bu	t-Bu	Me		30
Me	Me	Et	Me	74
Me	Me	i-Pr	Et	96
Me	Me	Et	i-Pr	64
Me	Et	Et	Me	74
Me	Et	i-Pr	i-Pr	62
Et	Et	Et	Me	60
Et	Et	i-Pr	i-Pr	62
i-Pr	Me	Et	Me	45
i-Pr	Me	Et	Et	36
i-Pr	i-Pr	i-Pr	Me	23
i-Pr	i-Pr	i-Pr	Et	29
i-Pr	i-Pr	Me	i-Pr	20
t-Bu	H	t-Bu	Me	34

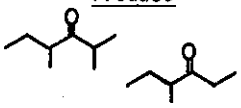
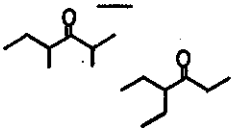
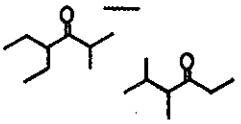
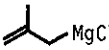
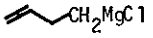
the reaction mixture is allowed to warm, rearrangement to the ketenimine 23 occurs. The second equivalent then adds to 23, affording an alkylated lithioenamine. This addition takes place at the 'carbonyl' carbon. A second addition α to this position occurs if 24 is quenched with an alkyl halide. Acid hydrolysis then gives the α,α,α-trisubstituted ketone 25. Alternatively,

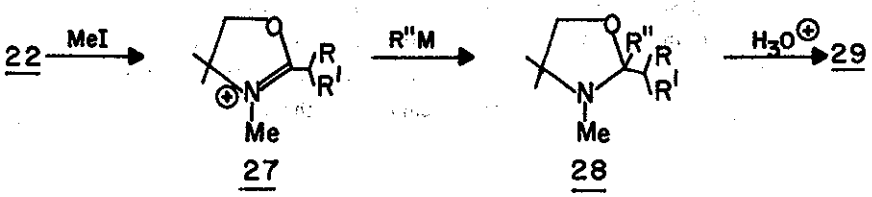
24 can itself be hydrolyzed to 26, an α,α-disubstituted ketone.

A similar ketone synthesis was accomplished by reacting the methiodide 27 of 22 with organometallic compounds[7]. Acid treatment of the adduct 28 gave the ketone 29. This procedure was extended to allylic Grignards, but in many instances, olefin isomerization led to mixtures of products[8] (Table 5).

Table 5

Ketones synthesized from 2-oxazoline methiodides (27)

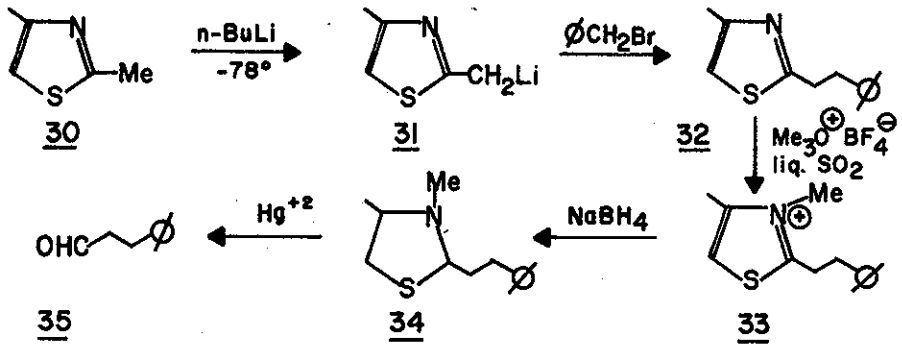
R	R'M	R"M	% 29	Product
Me	Et	i-PrLi	76%	
Me	Et	EtMgBr	64	
Me	Et	t-BuMgBr	0	—
Me	Et	i-PrMgBr	93	
Et	Et	EtMgBr	77	
Et	Et	t-BuMgBr	0	—
Et	Et	i-PrLi	88	
i-Pr	Me	EtMgBr	73	
i-Pr	Me	t-BuMgBr	0	—
Me	Et		38	sec-Bu-C(=O)-CH=C(CH$_3$)$_2$
			62	sec-Bu-C(=O)-CH$_2$-C(CH$_3$)=CH$_2$
Me	Et		88	sec-Bu-C(=O)-CH=CHCH$_3$
Et	Et		72	Et$_2$CH-C(=O)-CH$_2$CH=CHCH$_3$ (c & t)
			28	Et$_2$CH-C(=O)-CH(CH$_3$)CH=CH$_2$



It should also be noted that 2-oxazolines yield carboxylic acids if they are hydrolyzed without prior reduction by sodium borohydride[9]. This heterocycle serves as a precursor to this class of compounds, as well as being a protecting group for them, since they are inert to Grignard reagents. Also, esters can be generated if the oxazoline is hydrolyzed in an alcoholic medium. No further discussion of this application will be presented, as this survey is intended to deal specifically with processes culminating in aldehydes or ketones.

4) Thiazoles

Thiazoles have been employed in a sequence leading to aldehydes[10]. The scheme is similar to the synthesis of these compounds via 2-oxazolines, discussed above, and via dihydro-1,3-oxazines, which will be considered subsequently.



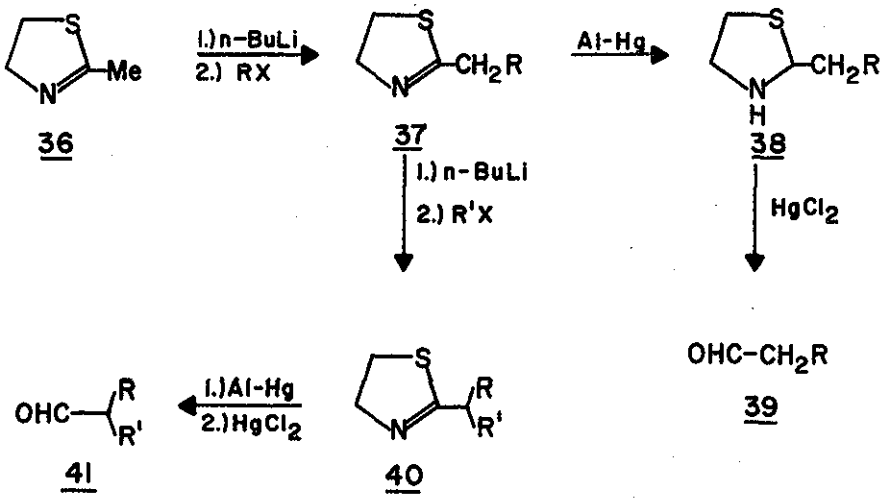
Proton abstraction from the 2-methylthiazole 30 was accomplished with n-butyllithium at -78° and the metallated species was alkylated with benzyl bromide. Quaternization at nitrogen, followed by reduction, gave the saturated heterocycle 34, a thiazolidine. The aldehyde was liberated under neutral conditions (an aqueous solution of mercuric salts), a valuable consideration when attempting the synthesis of acid-labile aldehydes.

In subsequent work by Meyers' group, alkylation was confirmed to occur at low temperatures (<-50°), but dimerization occurred if the reaction mixture was allowed to warm[11-13].

5) Thiazolines

In an analogous method to that just mentioned for thiazoles, 2-methylthiazoline 36 has been alkylated and converted to several aldehydes[14,14a].

Once again, n-butyllithium was used in conjunction with an alkyl halide, but the reduction of the C=N bond was accomplished with an aluminium-mercury amalgam. Primary or secondary alkyl iodides, benzyl chlorides, and allylic chlorides proved effective as electrophilic species. Alkyl bromides gave lower yields (55-65%) and alkyl chlorides afforded negligible alkylation (0-10%).



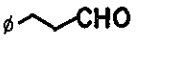
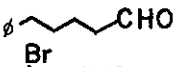
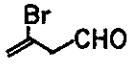
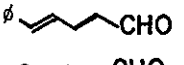
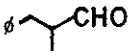
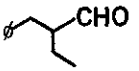
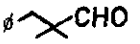
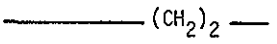
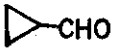
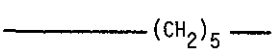
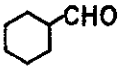
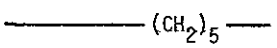
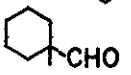
A second (or third) alkylation could be carried out prior to reduction, giving products with further substitution at the α-position. Masked cyclopropane- and cyclohexane-carboxaldehydes were prepared by reacting the anion of 36 with the appropriate dihalide and then adding a second equivalent of base. Reduction and cleavage yielded the free aldehydes.

In some instances, particularly in the preparation of trialkylated acetaldehydes, it was found that yields were improved by substituting lithium diisopropylamide for n-butyllithium.

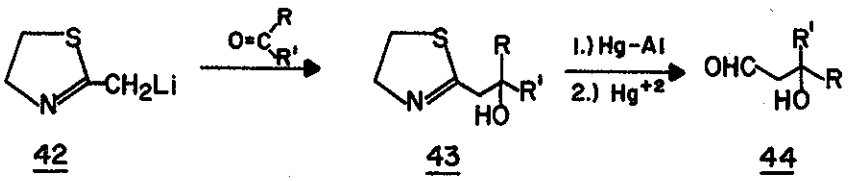
The monosubstituted products 39 were prepared in 50 to 60% overall yield.

Table 6

α-Substituted acetaldehydes from the thiazoline 36

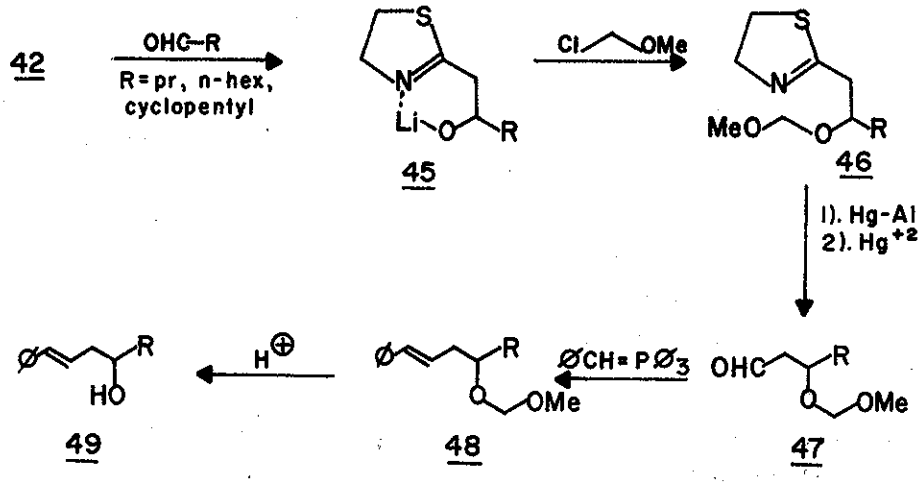
R	R'	R''	Aldehyde
ϕCH_2-	--	--	
$\phi(CH_2)_3$-	--	--	
CH_2=$CBrCH_2$-	--	--	
ϕCH=$CHCH_2$-	--	--	
n-Bu	--	--	
Me	ϕCH_2-	--	
ϕCH_2-	Et	--	
Me	Me	ϕCH_2-	
Me	Me	n-Bu	
		--	
		--	
		Me	

Because of the neutral conditions employed to unmask the aldehyde, Meyers' group extended the thiazoline route to the synthesis of β-hydroxy-aldehydes[15,15a]. Reaction of the lithio-thiazoline 42 with a carbonyl compound gave the hydroxythiazoline 43. Deblocking was accomplished as previously outlined, affording the β-hydroxyaldehyde 44. The common problems with this class of compounds, loss of water or reverse aldolization to acetaldehyde and the carbonyl component, were minimized through this technique.



42 43 44

A variation of this method allowed the synthesis[15,15a] of the homoallylic alcohols 49 from 42, as outlined below:



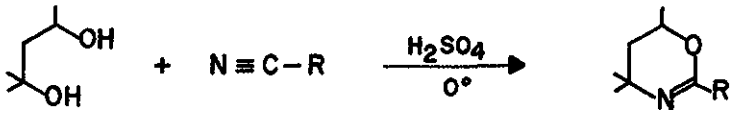
The alcohol function was most suitably protected by reacting the lithio adduct 45 with chloromethyl methyl ether.

6) Dihydro-1,3-oxazines

Dihydro-1,3-oxazines have proved extremely versatile in syntheses of aldehydes and ketones, for, according to the conditions employed, alkylation can be effected at the 'carbonyl' carbon, α to this site, or β to it[3].

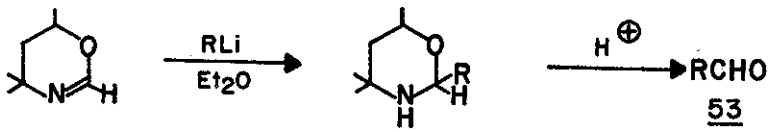
2-Substituted 4,4,6-trimethyldihydro-1,3-oxazines 50 are readily available[16-18], with most of the preparations involving condensation of

carboxylic acids, nitriles, or amides with amino alcohols, olefins, or glycols. In their extensive work on oxazine chemistry, Meyers' group found[19] the condensation of a glycol with a nitrile in sulphuric acid[16] to be the method of choice.



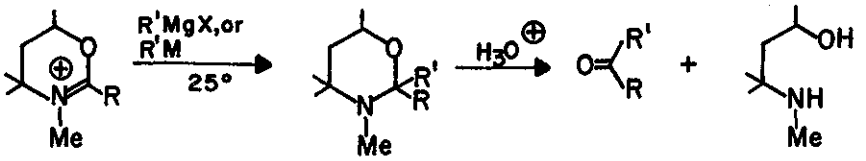
50

In the case of the oxazine 51, in which the 2-position is unsubstituted, treatment with an alkyl lithium reagent leads to the tetrahydro derivative 52[20]. This addition at the 'carbonyl' carbon provides an aldehyde synthesis, for this adduct yields 53 upon acid hydrolysis. The yields of 52 for R=n-Bu and t-Bu were 66% and 55%, respectively.



51 52 53

Although 2-substituted dihydro-oxazines are inert to Grignard attack, the electrophilicity of the 2-position can be enhanced to allow a ketone synthesis[21,22]. The methiodide(3) of 50 was found to react with organo-lithium or Grignard reagents to give the tetrahydro-oxazine 55, the equivalent of a 1,2-carbonyl addition. Acid hydrolysis then liberated the ketone. The yields for the sequence were dependent on the nature of the



54 55 56

(3) If a particular methiodide is non-crystalline, the corresponding methanesulfonate or fluoroborate salts may be used instead.

2-substituent (R) and on the organometallic employed. When R=Me, the Grignard was sufficiently basic to remove the α-proton, as well as add to the C=N link. Alkyl lithium reagents, being more basic, gave correspondingly lower yields of the ketone. However, they could be used successfully when the α-protons were less acidic (e.g. R=$CH_2CH_2\phi$).

Hindered Grignards tended to cause reduction of the double bond rather than add to it (Figure 1), and bulky reagents which could not reduce the C=N bond, such as phenylmagnesium bromide, did not react. The latter problem was circumvented by alkylating with phenyllithium or using 2-phenyloxazinium methiodide and the appropriate organometallic. A final limitation of this method is that all attempts to produce cyclic ketones have failed (Figure 2).

Table 7

Ketones from the reaction of the methiodide 54 with organometallic reagents

R	R'M	% 56
ϕCh_2CH_2-	EtMgBr	78%
ϕCH_2CH_2-	n-BuMgBr	71
ϕCH_2CH_2-	n-BuLi	51
ϕCH_2CH_2-	t-BuLi	29
ϕ-	EtMgBr	70
CH_2=$CHCH_2C(\phi)H$	MeMgBr	56
cyclopropyl	n-BuMgBr	35

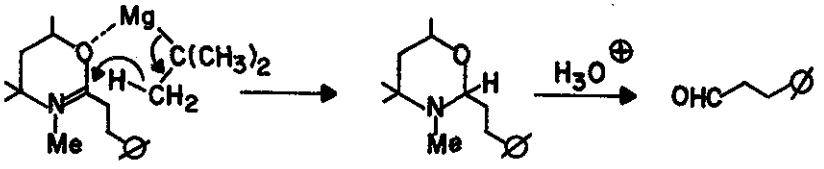


Fig. 1

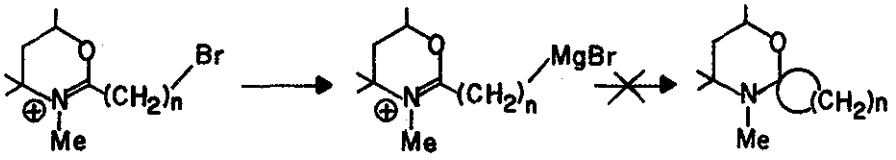
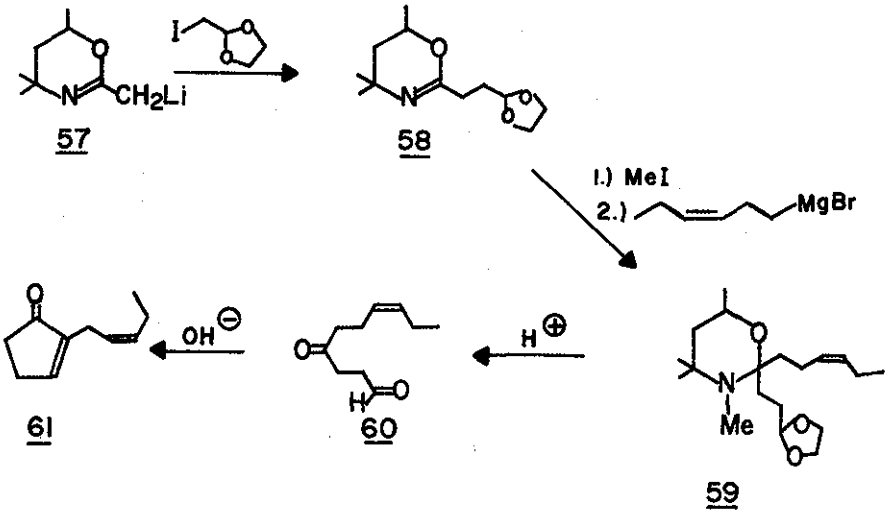


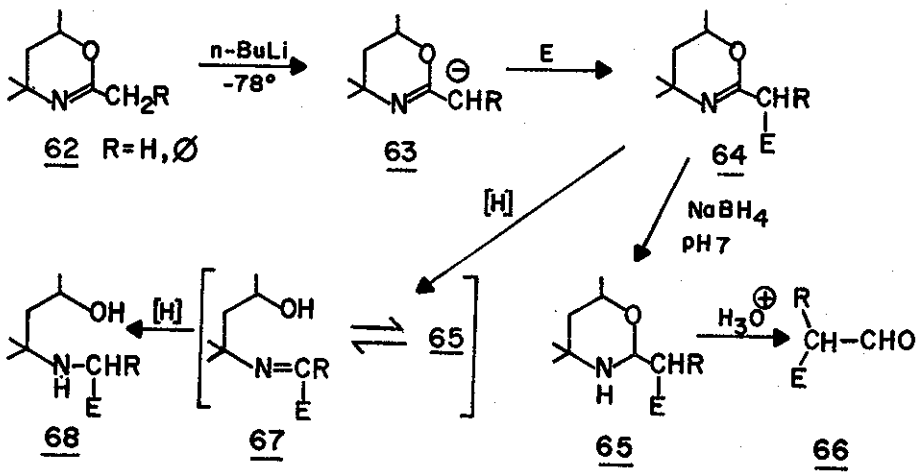
Fig. 2

A versatile synthesis of substituted cyclopentenones has been devised[23] using this approach, together with alkylation at the α position (the discussion of which follows). It is outlined below:



As with the 2-oxazolines, thiazoles, and thiazolines discussed previously, a carbanionic species 63 can be generated, allowing substitution α to the heterocycle by a variety of electrophiles[19,24,25]. Reduction to the tetrahydro-oxazine 65 was carried out with buffered sodium borohydride[(4)] (pH 5-8, pH 7 optimum), for catalytic or other metal hydride reductions gave

(4) Using sodium borodeuteride ($NaBD_4$), C-1 deuterioaldehydes were prepared via this route.



the amino alcohol 68, as a result of the ring tautomerism between 65 and 67. The aldehyde 66 was liberated with aqueous oxalic acid or 90% acetic acid.

Table 8

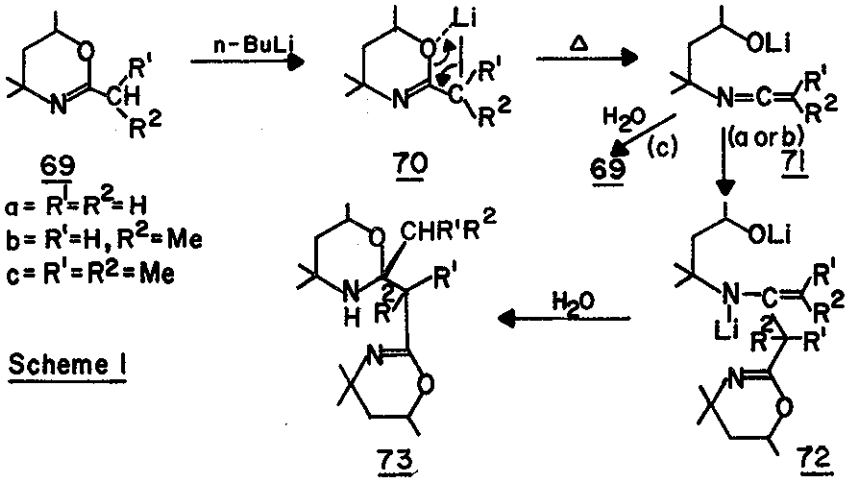
α,α-Disubstituted acetaldehydes from dihydro-1,3-oxazines

Oxazine	R'X(E)	% 66
62, R=H	MeI	60%
	n-PrI	65
	n-BuI	67
	allyl bromide	53
	2-bromoethyl ether	54
	i-PrI	47
	ϕCH_2Br	54
	3-bromocyclohexene	50
62, R=ø	MeI	70
	n-PrBr	69

In this sequence, the alkylation can only be carried out for a primary carbanion or when the carbanion is further stabilized (e.g. 62, R=ø, CO_2Et). With secondary and tertiary carbons, the anion is only formed at a temperature

at which it is unstable. Rearrangement ensues and alkylation cannot compete meaningfully (71 does not react with electrophiles). When the carbanion is primary or secondary, dimerization occurs at the elevated temperatures, as is represented in Scheme 1.

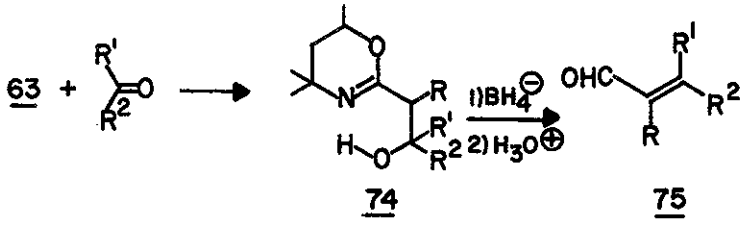
In the above synthesis (62→66), primary alkyl bromides and iodides gave good yields, although chlorides could be used if they were activated (e.g. ϕCH_2Cl, $CH_2=CHCH_2Cl$, $CH_3CH_2C\equiv CCH_2Cl$). However, secondary halides produced

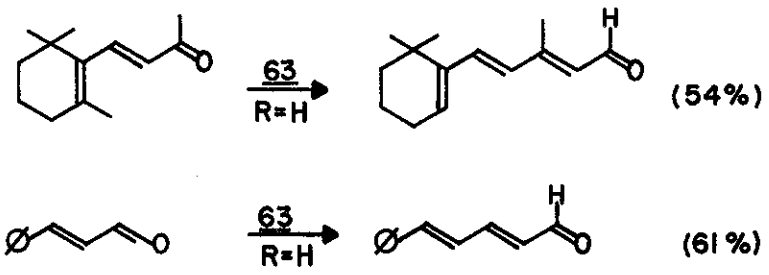


Scheme I

more elimination products with increasing steric bulk, as did homopropargyl or homoallyl halides. The only secondary halides found to give good yields were those derived from alicyclic systems, in which steric bulk is reduced.

α,β-Unsaturated aldehydes were prepared[19,26] by reacting various carbonyl compounds with the anion 63, followed by reduction and hydrolysis.





Similarly precursors to γ-hydroxyaldehydes and their γ-oxo derivatives were obtained[27] from the reaction of epoxides with 63.

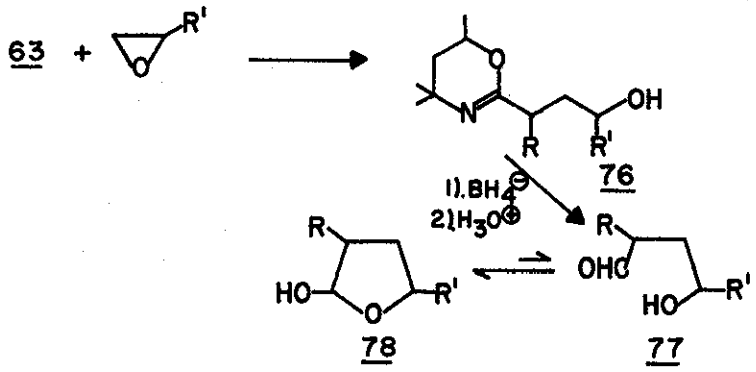


Table 9

Products from the reaction of various epoxides with the lithiated species 63

Oxazine	Epoxide	% (77 & 78)
63, R=H	ethylene	63%
	styrene	68
	cyclohexene	57
63, R=ø	ethylene	69
	styrene	61
	cyclohexene	59

For dihydro-oxazines in which the anion generated was further stabilized (e.g. 63, R=ø, CO_2Et), successive alkylations at this position could be carried out with dihalides, leading ultimately to alicyclic aldehydes[28]. The sequence is illustrated:

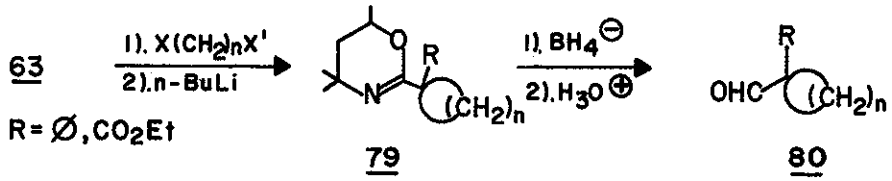
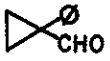
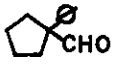
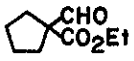
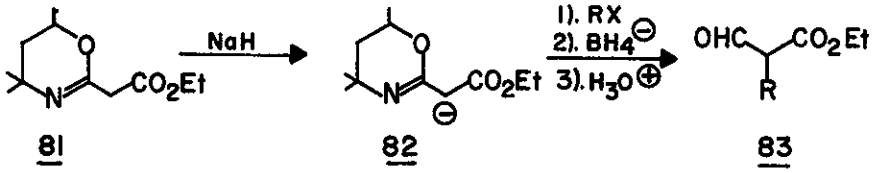


Table 10

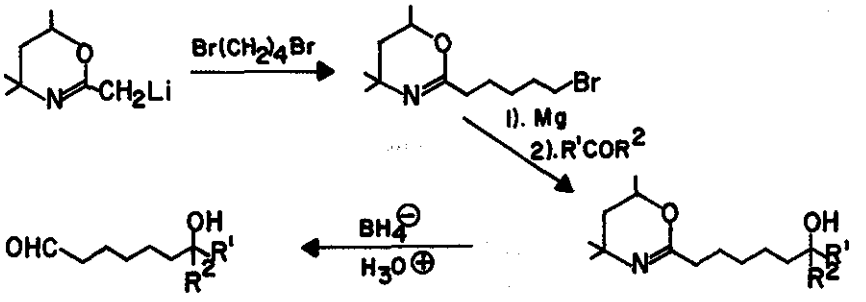
Alicyclic aldehydes from dihydro-1,3-oxazines

Oxazine	Dihalide	Aldehyde	% 80
63, R=ø	1,2-dibromoethane		62%
63, R=ø	1,3-dibromopropane		49
63, R=ø	1,4-dibromobutane		60
63, R=CO_2Et	1,4-dibromobutane		72

α-Formyl esters resulted from reaction of the anion of oxazines containing the carboethoxy group with alkyl halides, succeeded by the normal reduction and hydrolysis[19]. In this instance, sodium hydride was used to generate the doubly stabilized carbanion 82.

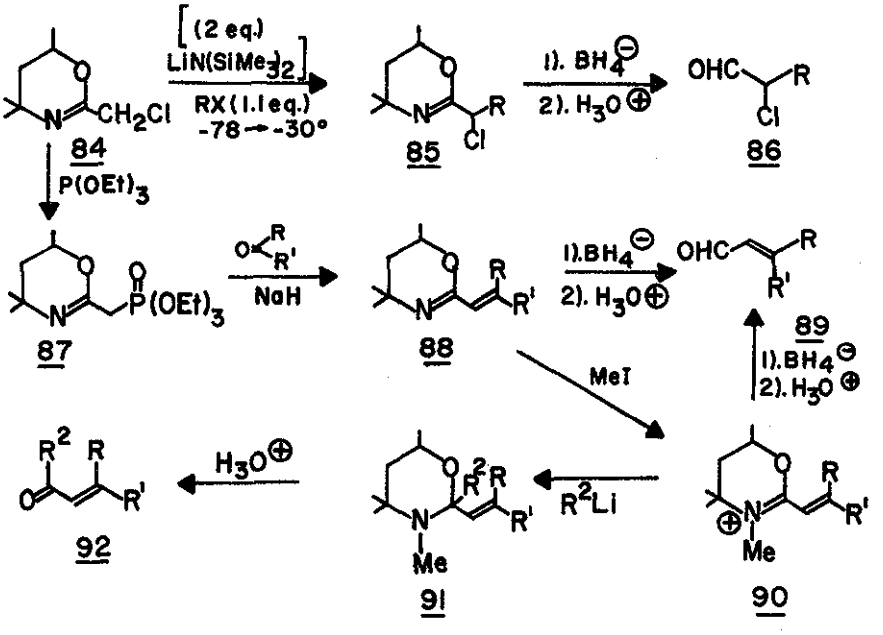


The oxazine carbonyl synthesis also allows elaboration of the side chain[19]. Since the heterocycle is inert to Grignards, these reagents can be used to modify other sites in the synthon. An example of this application is shown in Scheme 2.



Scheme 2

2-Chloromethyloxazine, 84, has recently been applied by Meyers et al. to the synthesis of α-chloroaldehydes and α,β-unsaturated aldehydes[29,30]. When 84 was treated with lithium bis(trimethylsilyl)amide (LiBSA) followed by an alkyl halide, the chloro-oxazine 85 was produced in high yield. This was transformed to the α-chloroaldehyde 86 by the usual methods[29].



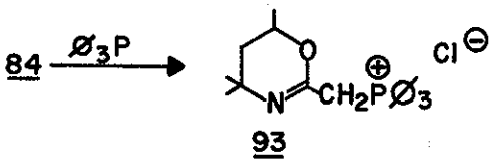
Alternatively, 84 could be converted into the phosphonate ester 87[30] which reacted with carbonyl compounds[31] giving unsaturated oxazines[(5)]. These in turn afforded the α,β-unsaturated aldehydes. Conjugated ketones were also prepared via the N-methyl quaternary salt 90. Alkyl lithium reagents added in the normal manner and acid hydrolysis gave 92. Overall yields ranged from 50 to 80%.

Table 11

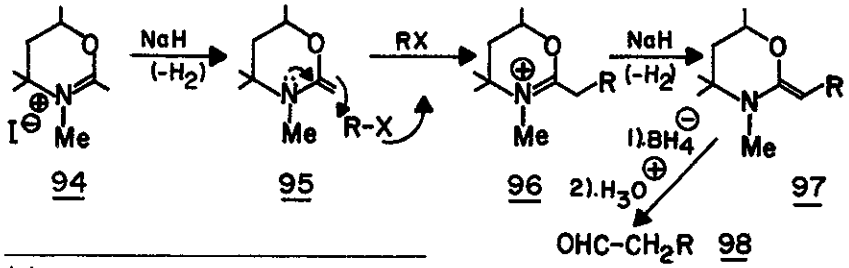
Product composition from the alkylation of 84 in lithium bis(trimethylsilyl) amide

RX	DHO-CH_2Cl (84)	DHO-CHRCl (85)	DHO⟨DHO
MeI	3%	97%	0%
EtI	0	100	0
EtBr	1	93	6
EtCl	16	7	77

(DHO = Dihydrooxazine)



A modification of the α-alkylation reaction has been devised which allows the manipulations to be performed at room temperature with sodium hydride instead of n-butyllithium[32]. The methiodide of the 2-methyloxazine, 94, thus yielded the enamine 95. Alkylation and reaction with the second equivalent of hydride ion gave 97, convertible to the corresponding aldehyde.



(5) The phosphonium salts 93 were found to give similar results to the phosphonate esters (Table 12).

Table 12

Vinyloxazines from phosphonate esters or phosphonium salts

R	R^1	R^2	% Vinyloxazines (88 or 91) from 87	from 93
ø	H	H	80%	94%
ø	Me	H	57 (24:76,c:t)	70 (50:50,c:t)
ø	ø	H	77	52
Me	Me	H	73	50
Et	H	H	75	80
n-hexyl	H	H	72	82
$-(CH_2)_4-$		H	77	48
$2\text{-}C_5H_4N$	H	H	65	72
H	ø	Me		
Me	Me	Et		
$-(CH_2)_4-$		Et		

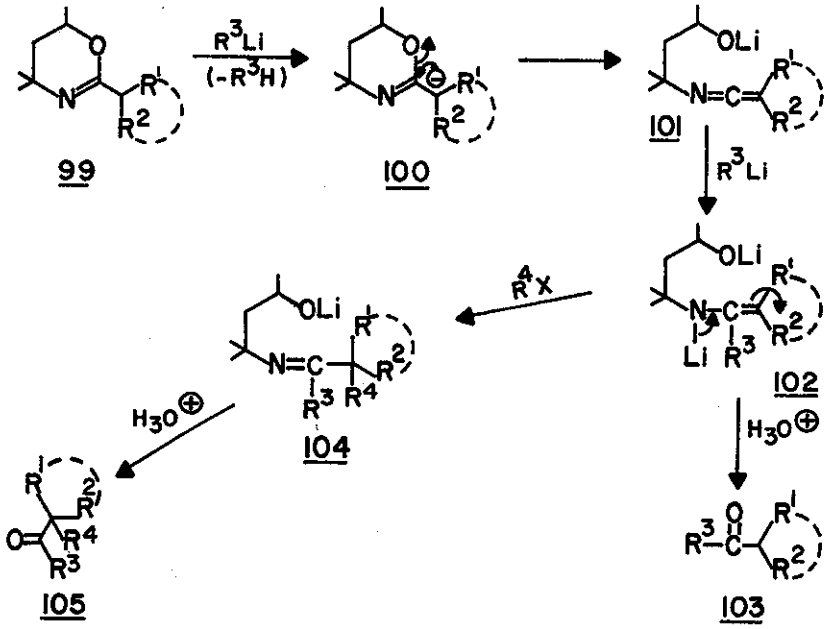
Table 13

Substituted acetaldehydes via alkylation of 94
(using sodium hydride)

RX	Aldehyde (98)	Yield
$ø(CH_2)_3I$	$OHC(CH_2)_4ø$	51%
$H_2C=C(Br)CH_2Br$	$OHC(CH_2)_2C(Br)=CH_2$	60
$øCH_2Br$	$OHCCH_2CH_2ø$	58

The instability of the oxazine carbanion 100 at elevated temperatures ($\sim$0-10°), which results in rearrangement to the ketenimine 101, provides another route to ketones[33,34]. Two equivalents of the organolithium base are used; the first generates the anion 100 and the second adds to 101 to give 102, a metallated enamine. Hydrolysis of this compound results in the α,α-disubstituted ketone 103, or it can be reacted with an alkyl halide, producing an intermediate which ultimately gives the ketone 105 with a

quaternary carbon α to the carbonyl. The alkylation occurs at the most substituted carbon, in contrast to the prior results of Stork[35].



Oxazines can also be alkylated β to the masked carbonyl group if the 2-vinyloxazine 106 is employed. While 106 polymerizes when treated with organometallic reagents[19], 108 can be prepared in reasonable yields (Table 15) if an alkyl halide is added to 106 prior to the introduction of the Grignard reagent[36,37]. The halide serves to trap the initially formed magnesium salt. Reduction and hydrolysis result in the aldehyde 109, a

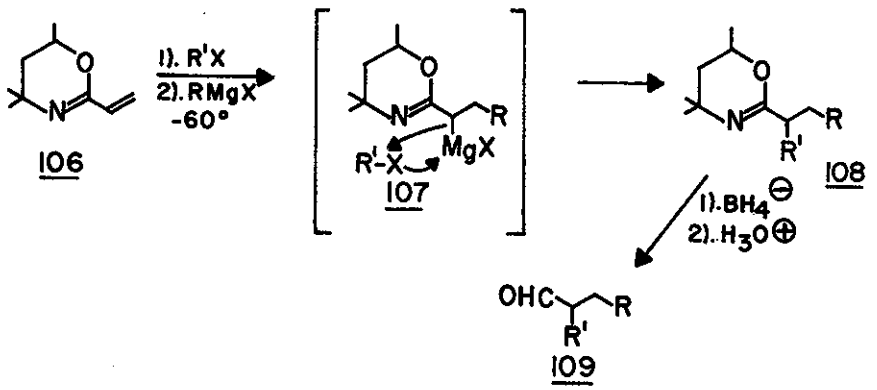
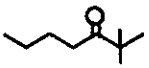
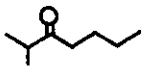
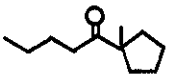
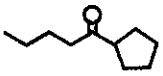
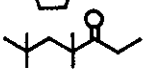
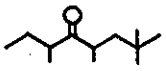
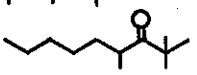
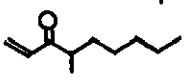
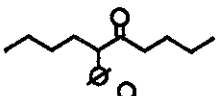
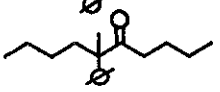


Table 14

α-Disubstituted and α-trisubstituted ketones from dihydro-1,3-oxazines

R^1	R^2	R^3Li	R^4X	Ketone (103 or 105)	Yield
Me	Me	øLi	EtI		50%
Me	Me	n-BuLi	MeI		60
Me	Me	n-BuLi	-		73
—$(CH_2)_4$—		n-BuLi	MeI		63
—$(CH_2)_4$—		n-BuLi	-		58
Me	neopentyl	EtLi	MeI		65
Me	neopentyl	sec-BuLi	-		63
Me	n-amyl	t-BuLi	-		53
Me	n-amyl	CH_2=CHLi	-		45
ø	n-butyl	n-BuLi	-		77
ø	n-butyl	n-BuLi	Me		63

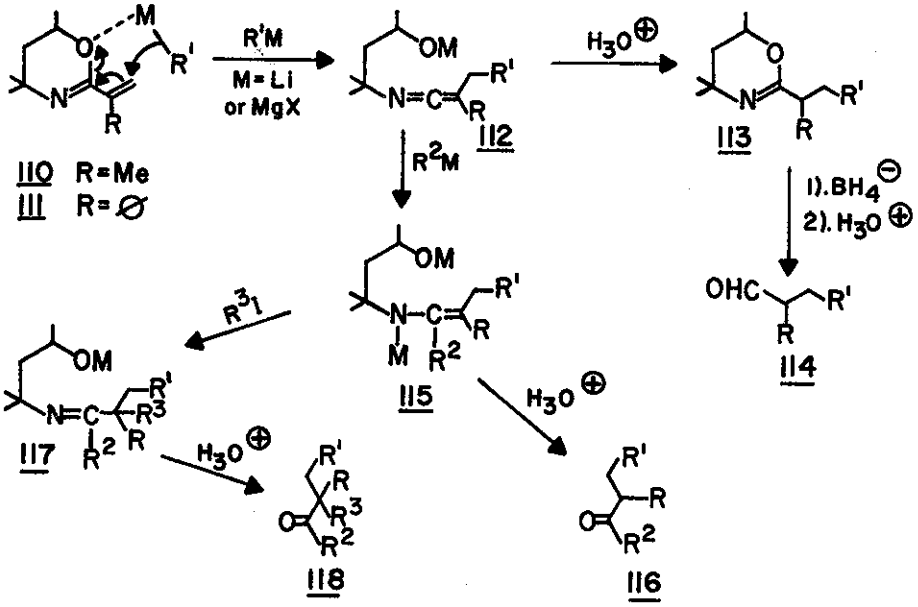
compound which has been alkylated α and β to the carbonyl group.

While 106 is polymerized by organometallics, its substituted derivatives, 2-isopropylidene-oxazine 110 and 2-(α-styryl)-oxazine 111, react under the same conditions to give a ketenimine 112[38-40]. This can be hydrolyzed to the substituted dihydro-1,3-oxazine 113 and subsequently transformed to the aldehyde 114, or alkylated as described above to give the α,α-disubstituted product 116 or the α-(quaternary carbon) ketone 118.

Table 15

Aldehydes prepared via the vinyloxazines 106

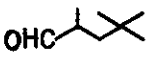
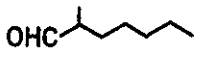
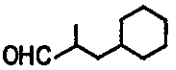
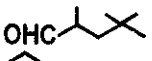
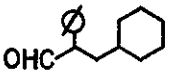
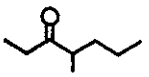
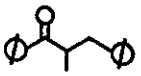
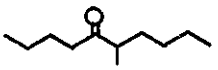
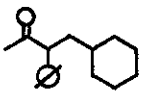
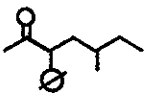
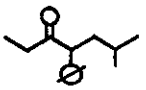
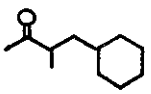
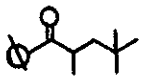
RMgBr	R'X	% 109
øMgBr	MeI	71%
øMgBr	ϕCH_2Br	60
øMgBr	CH_2= $CHCH_2Br$	43
øMgBr		44
øMgBr	EtI	31
CH_3MgBr	ϕCH_2Br	26
EtMgBr	ϕCH_2Br	72
CH_2=$CHCH_2MgBr$	ϕCH_2Br	31



Thus, the above sequences involve the equivalent of 1,4-addition to an α,β-unsaturated carbonyl compound.

Table 16

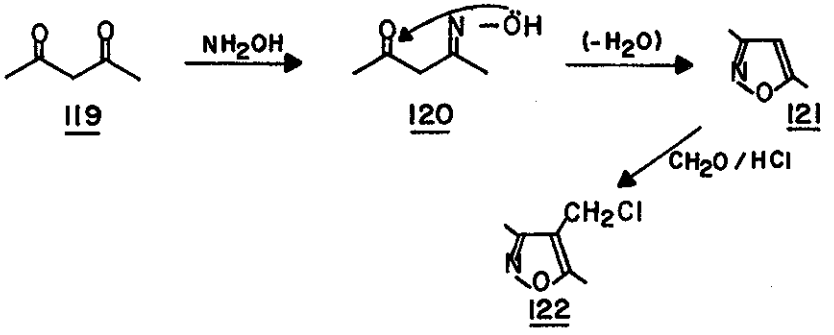
Aldehydes and ketones synthesized from the vinyloxazines 110 and 111

R	R^1M	R^2M	Product	Yield
Me	t-BuLi			43%
Me	n-BuLi			32
Me	$C_6H_{11}MgBr$			78
Me	t-BuLi			71
ø	$C_6H_{11}MgBr$			94
Me	EtMgBr	EtMgBr		67
Me	øMgBr	øMgBr		47
Me	n-BuLi	n-BuLi		79
ø	$C_6H_{11}MgBr$	MeLi		79
ø	sec-BuLi	MeLi		65
ø	i-PrBuLi	EtMgBr		65
Me	$C_6H_{11}MgBr$	MeLi		82
Me	t-BuLi	øMgBr		31

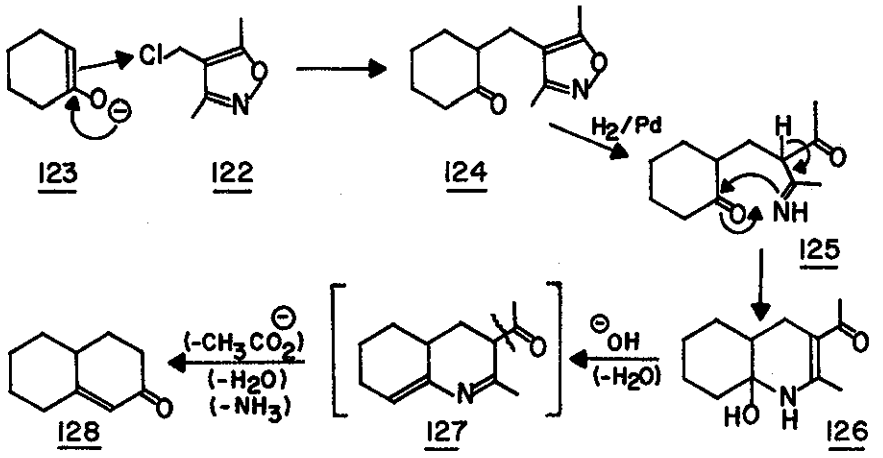
7) Isoxazoles

Isoxazole derivatives have proved useful in the synthesis of polycyclic carbonyl compounds, and, in particular, have been employed in two steroid syntheses[41-43]. Alkylation of an isoxazole is the equivalent of alkylation β to the carbonyl.

Condensation of the diketone 119 with hydroxylamine leads to 3,5-dimethylisoxazole 121, which gives the required heterocycle 122 on chloromethylation[44]. 122 reacts with enolates, giving 124, which is ultimately converted into the α,β-unsaturated ketone 128[45]. The mechanisms for these

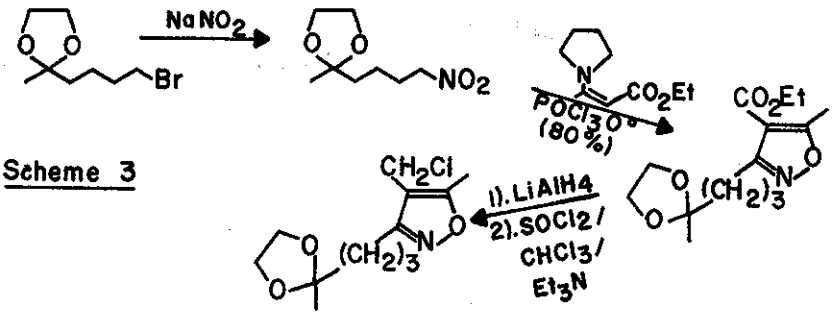


transformations are shown below:



After 124 is generated, catalytic hydrogenation cleaves the N-O bond to give the imino ketone 125, which in turn cyclizes to 126. Basic hydrolysis of this compound produces a masked triketone 127. Loss of acetate from, and cyclization of, this intermediate yield 128. The sequence of steps for the conversion of 127 to 128 is not known.

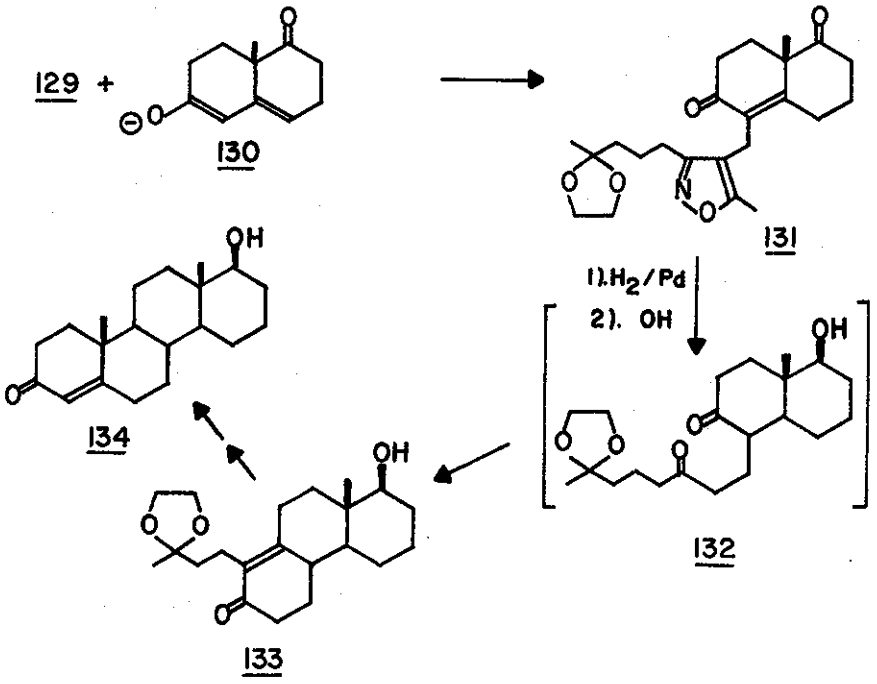
The isoxazole 129[46], the synthesis of which is depicted in Scheme 3, was used in the construction of the A and B rings of dl-homotestosterone 134[41]. Alkylation of the bicyclic enolate 130 afforded the intermediate 131. Hydrogenation followed by treatment with base caused cyclization of



Scheme 3

129

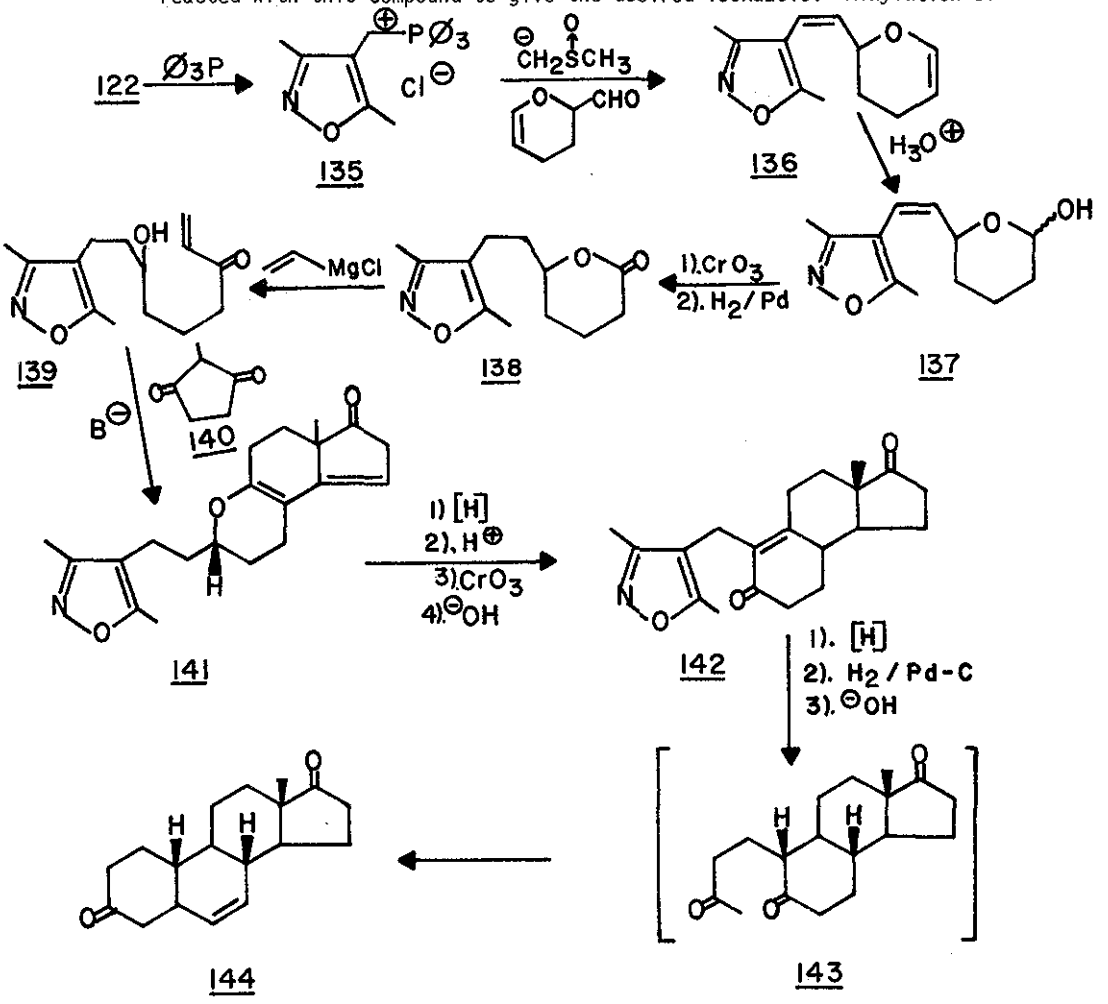
the B ring to give 133 via the diketone 132. Known procedures allowed the conversion of 133 to dl-homotestosterone. The yield for the conversion of



131 to 133 was 60%, and dl-homotestosterone was prepared from 133 in 74% yield.

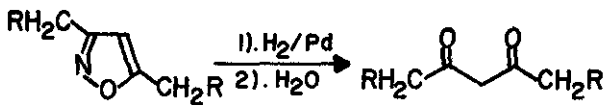
The second steroid synthesis had as its key intermediate the isoxazole 139, which was used to alkylate the 5-membered cyclic diketone 140[42,43]. This ketone formed the D-ring of the steroid 144.

Treatment of the previously described isoxazole 122 with triphenyl phosphine formed its phosphonium salt, which underwent a Wittig reaction with 2-formyldihydropyran. Hydration of 136, followed by oxidation and hydrogenation yielded the saturated lactone 138. Vinylmagnesium chloride reacted with this compound to give the desired isoxazole. Alkylation of



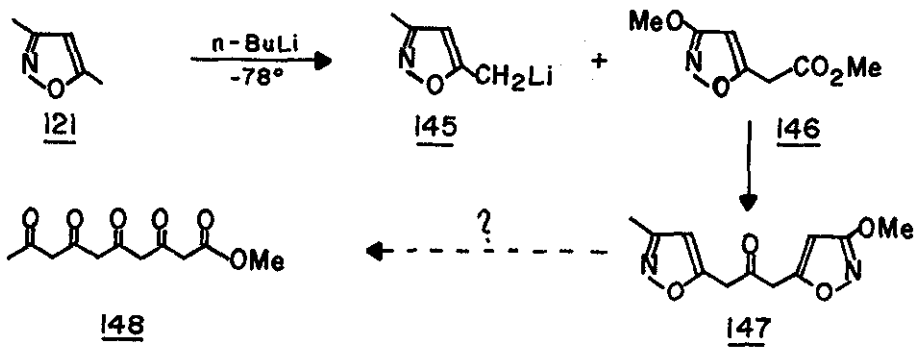
139 was successful, forming the enol ether 141. The D ring olefin was reduced, after which hydrolysis of the enol ether Jone's oxidation and cyclization gave the α,β-unsaturated ketone 142. Reduction of this olefin, catalytic cleavage of the isoxazole ring, and hydrolysis resulted in a transient triketone 143 which formed the desired steroid 144. It should be noted that the isoxazole ring was stable to all reaction conditions employed until it came time to liberate the masked carbonyl.

Isoxazoles can also be converted to β-dicarbonyl compounds (Scheme 4). Polyketo compounds such as 148 are of interest from a biosynthetic viewpoint



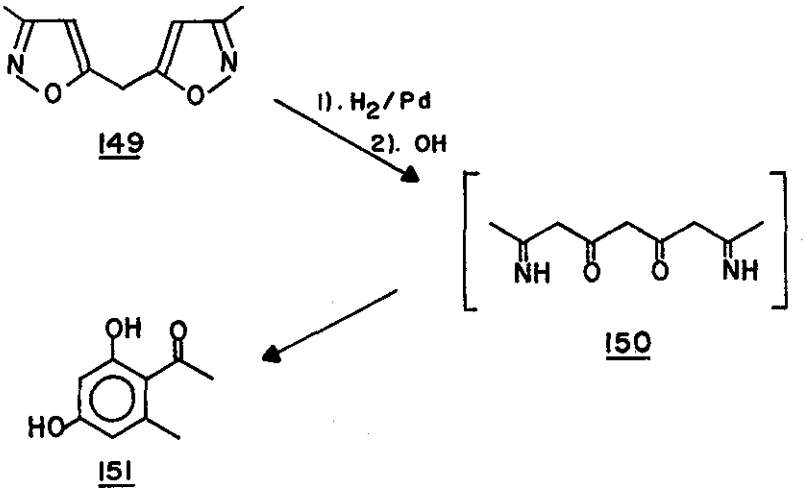
Scheme 4

and there have been recent efforts to realize them via isoxazoles[47,48]. Condensation of the lithio isoxazole 145 with 146 yielded the keto-bis-isoxazole 147, which can be viewed as a masked form of the tetraketo-ester



148. 145 was prepared by treating 121 with n-butyllithium at -78°. As yet, no report has been made of the actual conversion of 147 to 148.

Similarly, the bis-isoxazole 149 has been prepared[48], hydrogenolysis and hydrolysis of which gave the acetophenone derivative 151, presumably via the intermediate 150.

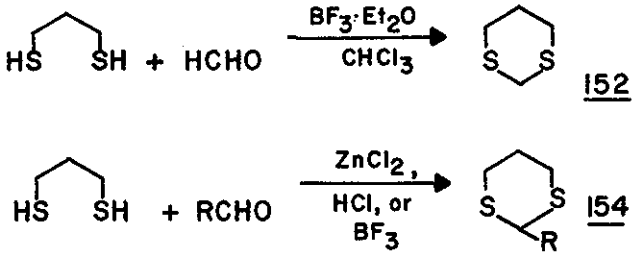


Heterocycles Yielding Reverse Carbonyl Charge Polarization

1) 1,3-Dithianes

The 1,3-dithiane system was first used as a synthetic tool in 1965[49] and has since found extensive use as a masked carbonyl capable of reacting with electrophiles[50]. This amounts to an alkylation at the carbonyl carbon. Thus this heterocycle is valuable in modifying the reactivity of the carbonyl group as well as being an alternative protecting group which allows regeneration of a specific carbonyl when used in conjunction with ethylene ketals (for example).

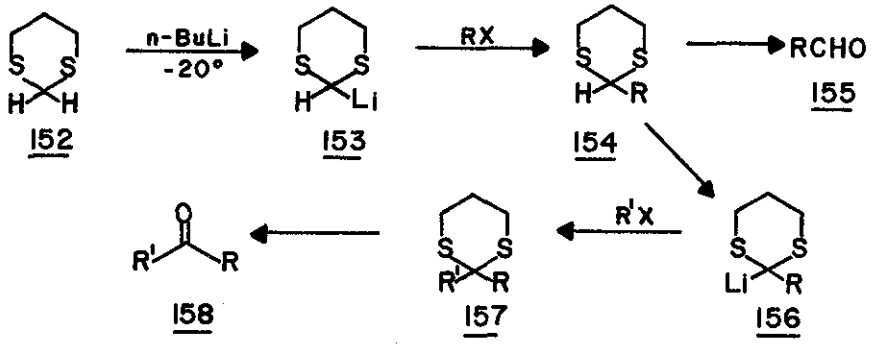
1,3-Dithiane, 152, can be prepared[51] by the Lewis acid catalyzed reaction of propan-1,3-dithiol with formaldehyde. Mono-substituted dithianes 154 are similarly available[50] (Scheme 5) or can be synthesized by alkylation of 152, as is described subsequently.



Scheme 5

The lithio dithiane 153, or the lithio monoalkyldithiane 156, both of which are generated from the corresponding dithiane with n-butyllithium reacts readily with various halides and when the product is hydrolyzed the aldehyde 155 or ketone 158, respectively, is liberated[49,50].

Hydrolysis of the dithiane is generally accomplished under neutral



conditions, making cleavage compatible with ethylene ketals and other acid labile protecting groups. A variety of methods for this operation have been reported[50,52-60]; commonly, aqueous mercuric oxide-mercuric chloride or calcium carbonate-mercuric chloride was used, but other methods have been introduced in efforts to improve yields and utilize less expensive reagents. Some of the hydrolytic reagents which have proved useful are presented in Table 17. Seebach's review of dithiane chemistry[50] gives additional data. The dithiane can also be cleaved with Raney nickel to give an alkane, but this falls outside the scope of this paper and will not be elaborated upon.

The versatility of the dithiane system has been exploited to produce a wide variety of carbonyl compounds, and some of the reaction possibilities are summarized in Table 18. All these examples are from work performed up to 1969 and this period in the dithiane field has been reviewed by Seebach[50]. Recently, a further review of dithiane chemistry has appeared[50a]. Some of the 'highlights' of recent efforts in dithiane chemistry will be discussed below without detailed examination of the early work.

Optically active aldehydes and ketones have been prepared by reaction of a dithiane with an optically active halide[62,63]. The iodide 160, prepared from (S)-2-methyl-1-butanol 159, reacted with the lithio dithiane to give 161.

Table 17

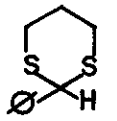
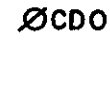
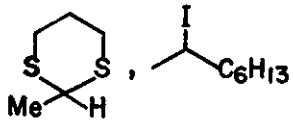
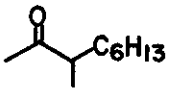
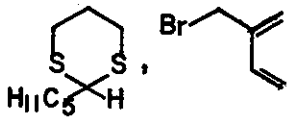
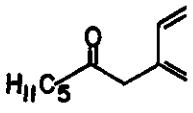
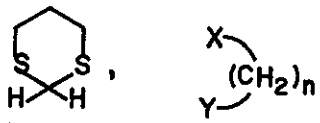
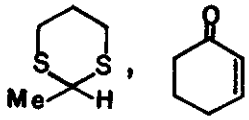
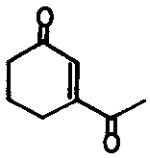
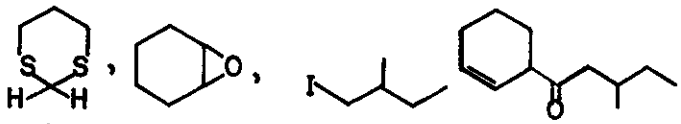
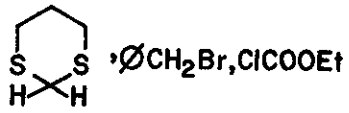
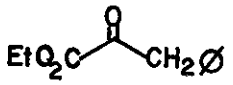
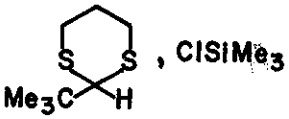
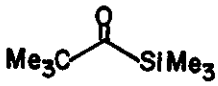
Reagents employed for the hydrolysis of 1,3-dithianes

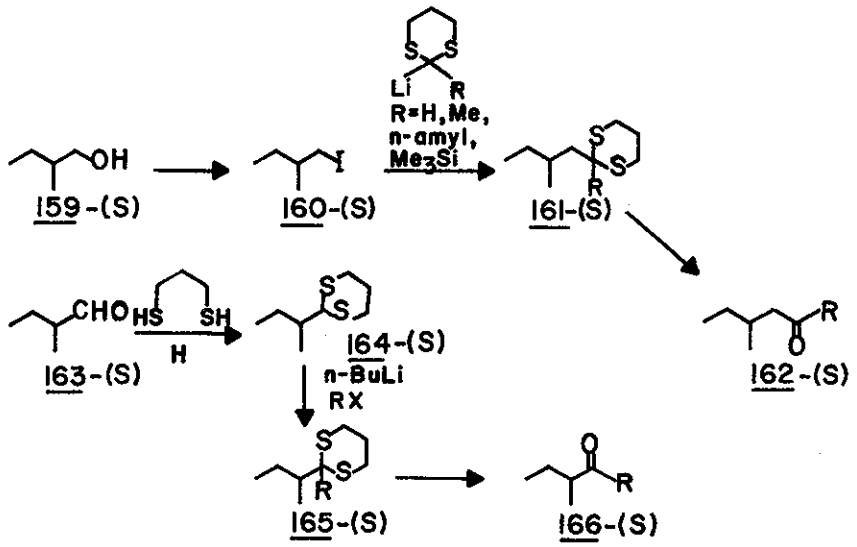
Reagent	Conditions	Yield	Reference
$HgCl_2$	90% MeOH or THF 2-4h reflux	63-87%	50,52
$HgCl_2$-HgO	90-94% MeOH 1-5h reflux	60-83%	50,52
$HgCl_2$-$CaCO_3$	80% MeCN or 90% MeOH	90-93%	50,52
$HgCl_2$-$CdCO_3$	øH/acetone/H_2O, 20h, 20°	34%	50
NBS	96% acetone, 5 min, -5 to -10°	76-97%	50,52
NBS-$AgNO_3$	aqueous CH_3CN or acetone		52
NCS-$AgNO_3$	aqueous CH_3CN or acetone	72-94%	50,52
HgO-BF_3	H_2O-THF,RT, few min	60-90%	53
$CuCl_2$-CuO	99% acetone, 1h reflux	80-90%	54
MeI-(CO_3^{-2})	moist acetone, reflux sev. h	71%	55
Ceric ammonium nitrate	75% CH_3CN,RT, 3 min	70-85%	56
Tl(III)trifluoroacetate	RT, 5 min	77-80%	57
$MeFSO_3/^{\ominus}OH$	RT, 1h	62-88%	58
H_2SO_4	RT, 20 min	91-95%	59
O-mesitylenesulphonyl-hydroxylamine	1) $CHCl_3$,RT, 30-60 min 2) H_2O	21-74%	60

This was hydrolyzed to the (S)-aldehyde or (S)-ketone 162 in high optical yield. Also, 159 was oxidized to the aldehyde 163 which was reacted with propan-1,3-dithiol to give 164. Alkylation and hydrolysis afforded 166. *Only 20% loss of activity resulted from this sequence, in which the* alkylation was α to the asymmetric centre.

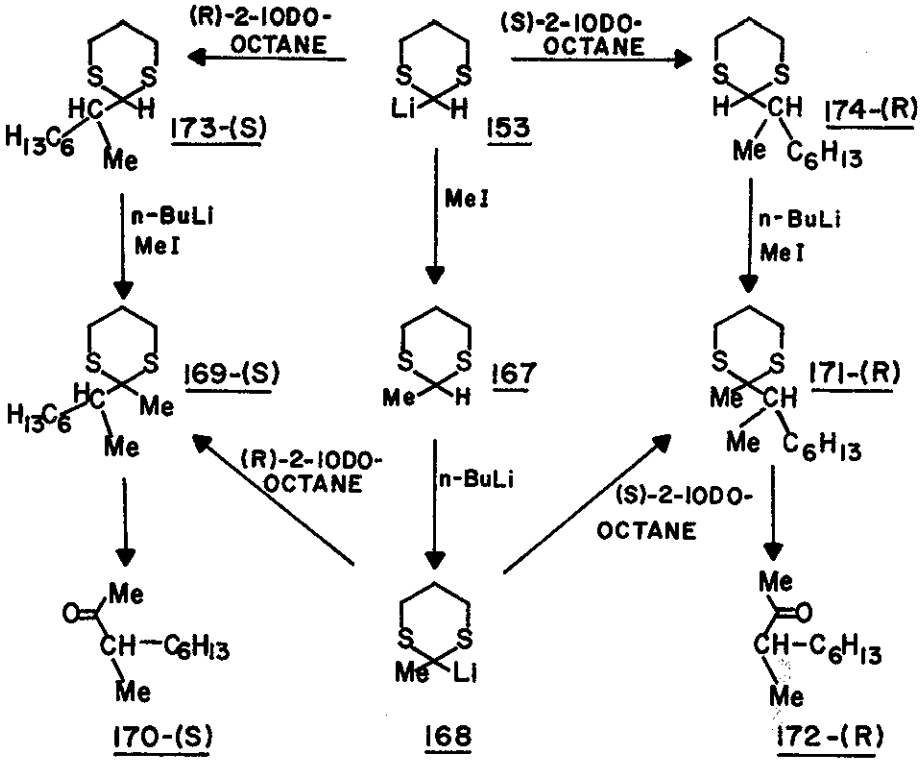
Table 18

Some representative carbonyl compounds synthesized from 1,3-dithianes

Reactants	Final Product	Reference
		61
		63
		64
		51,65
		50,52,66
		62
		50
		67

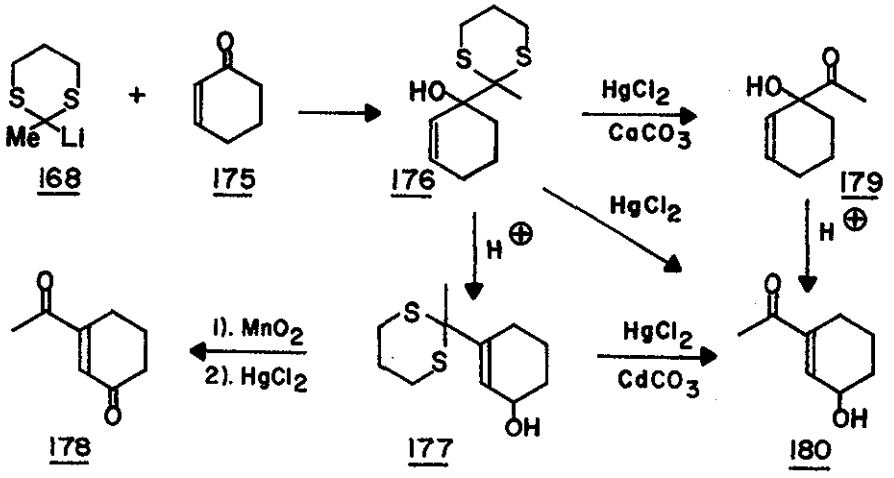


In cases where alkylation occurs by Sn^2 displacement at the asymmetric centre, inversion of configuration occurs. The optical yield is approximately



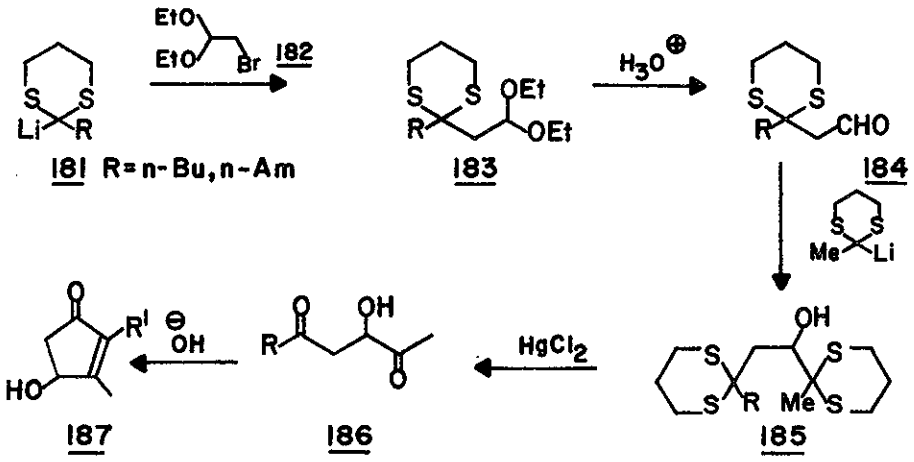
10% higher when the active halide is used to alkylate the lithio methyldithiane 168, rather than 153. It was reasoned[63] that the methyl group caused a higher degree of inversion in the alkylation.

The lithio methyldithiane 168 has been reacted with carbonyl compounds to produce polyfunctional ketones[52,66]. Condensation of 168 with cyclohexenone led to the highly acid labile adduct 176. In the presence of acid, it rearranged to another allylic alcohol, 177. Oxidation with manganese dioxide and hydrolysis of the dithiane yielded the diketone 178. 176 proved to be so sensitive to acid that when it was hydrolyzed with mercuric chloride, it was isomerized by the traces of hydrogen chloride liberated. This could be prevented by using an acid scavenger such as calcium carbonate. In this instance 179 was the product.

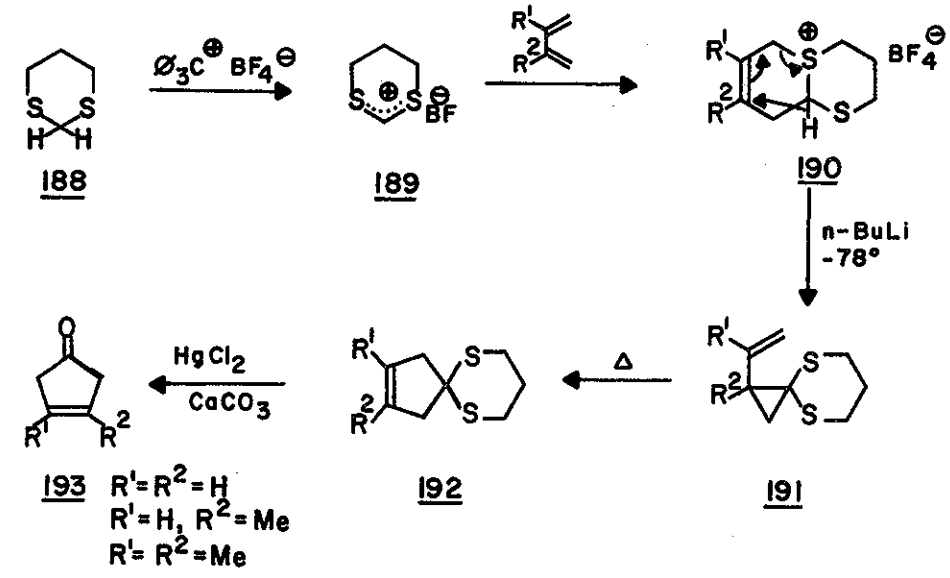


Dithianes also show promise in the synthesis of prostaglandins. Woessner and Allison have synthesized the hydroxycyclopentenone 187 using the dithiane moiety as the key tool[68]. 181 was alkylated with the diethyl acetal of bromoacetaldehyde and the adduct 183 was hydrolyzed to the corresponding aldehyde. Reaction of 184 with lithio methyldithiane yielded the hydroxy-bis(dithiane) 185, which was then deblocked and cyclized to 187. The acetal and dithiane perform complementary roles as protecting groups in this efficient synthesis, which has as one of its intermediates an acid

labile α-hydroxyketone 186.



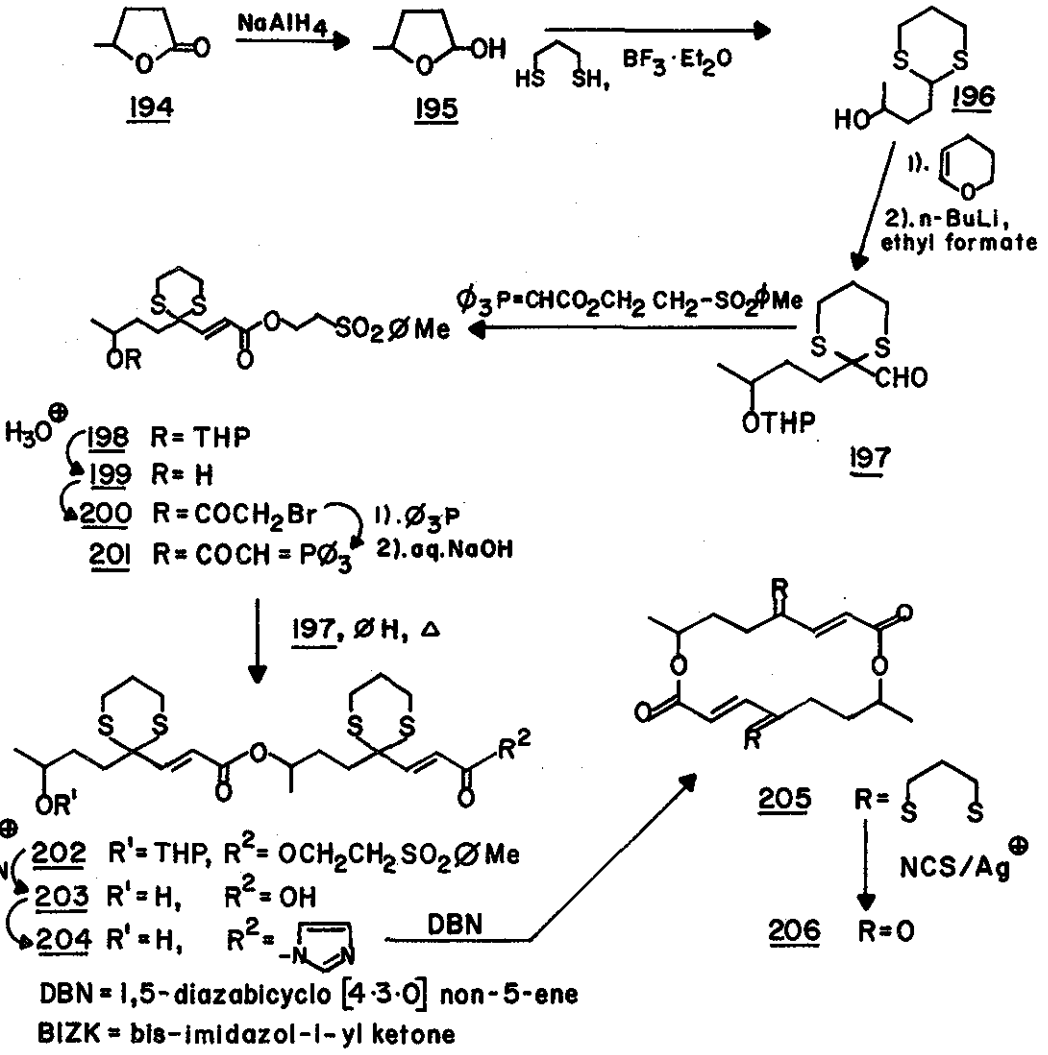
When 1,3-dithiane is treated with the fluoroborate of triphenylfluoromethane, the 1,3-dithienium salt 189 is formed[69]. It in turn reacts with dienes in a cycloaddition process to give 190. A rearrangement product, a



vinylcyclopropane 191, then results from n-butyllithium treatment and this compound yields a spirodithiane when heated. As 192 is hydrolyzed under neutral conditions, an unsaturated ketone 193 is formed with no rearrangement to conjugated material. Calcium carbonate is used with the mercuric chloride to mop up the small amounts of acid released in the hydrolysis.

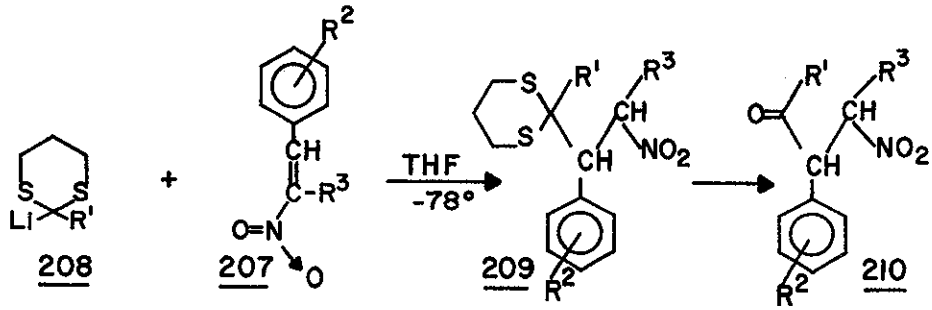
In the above sequence, 189 is in effect a masked form of carbon monoxide.

The 1,3-dithiane heterocycle has been applied to the synthesis of the macrolide antibiotic pyrenophorin, 206[70]. Reduction of the lactone 194 gave



the hemi-acetal 195 which was simultaneously opened and converted to the dithiane alcohol 196. Hydroxyl protection and formylation yielded 197. A series of transformations gave 201 which underwent a Wittig reaction with 197 to produce 202. Further manipulations gave 204 which could be lactonized to yield 205. Deblocking in N-chlorosuccinamide-silver nitrate gave the desired macrolide 206.

Seebach and Leitz have accomplished[71] the 1,4-addition of 2-lithio-1,3-dithianes to substituted ω-nitrostyrenes 207 to give adducts of type 209.



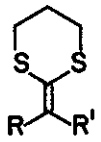
Note, however, that this is still an alkylation at the masked carbonyl. Typical results are presented in Table 19, but the authors reported that yields had not been optimized in many instances.

Table 19

Structures and yields of nitrodithiane adducts (209)

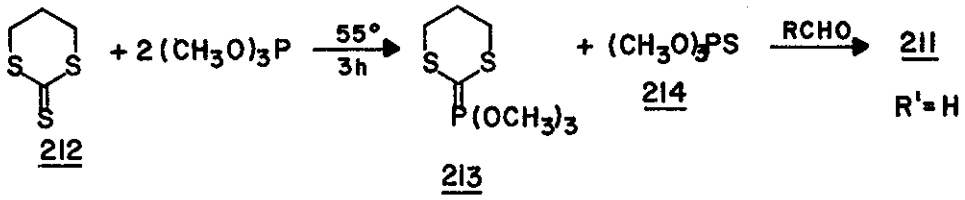
R^1	R^2	R^3	% 209
H	4-CH_3O	H	25%
H	2,5-$(CH_3O)_2$-4-Me	H	90
H	4-CH_3O	Me	50
H	2,5-$(CH_3O)_2$-4-Me	Me	70
Me	4-CH_3O	H	25
ø	4-CH_3O	H	90
ø	2,5-$(CH_3O)_2$	H	72

Much of the recent work in the dithiane field has involved compounds exemplified by 211, a ketene thioacetal. They had been prepared by Corey



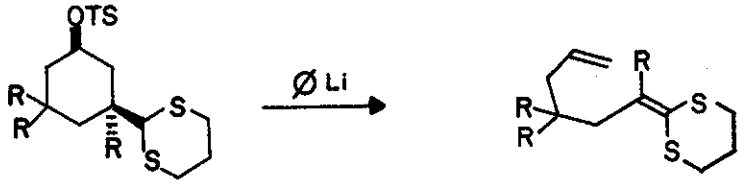
211

and Markl[72] via the Wittig reaction of an aldehyde with 213. This is not a general procedure for it is unsuccessful with ketones, even under forcing conditions. Also, there is the problem of contamination with 214.



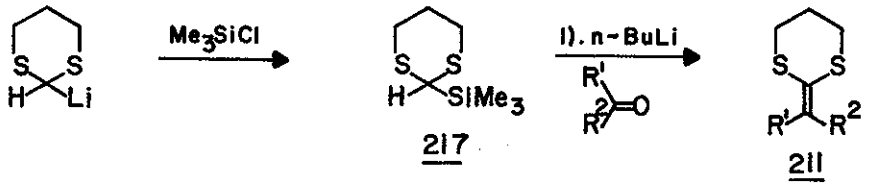
212 213 214 211

Another non-general route to ketene thioacetals was discovered by Marshall and Belletire[73]. Treatment of the tosylate 215 with phenyl lithium caused the elimination reaction shown, to produce 216. This was accomplished for R=H,CH_3.



215 216

A more useful procedure was arrived upon by several groups[74-78] in quick succession. Reaction of 2-lithio-1,3-dithiane with trimethylsilyl chloride gave 217. The anion generated from this compound with n-butyllithium reacted with either aldehydes or ketones to give the ketene thioacetal 211. Some examples, along with the yields obtained, are presented in Table 20.



217 211

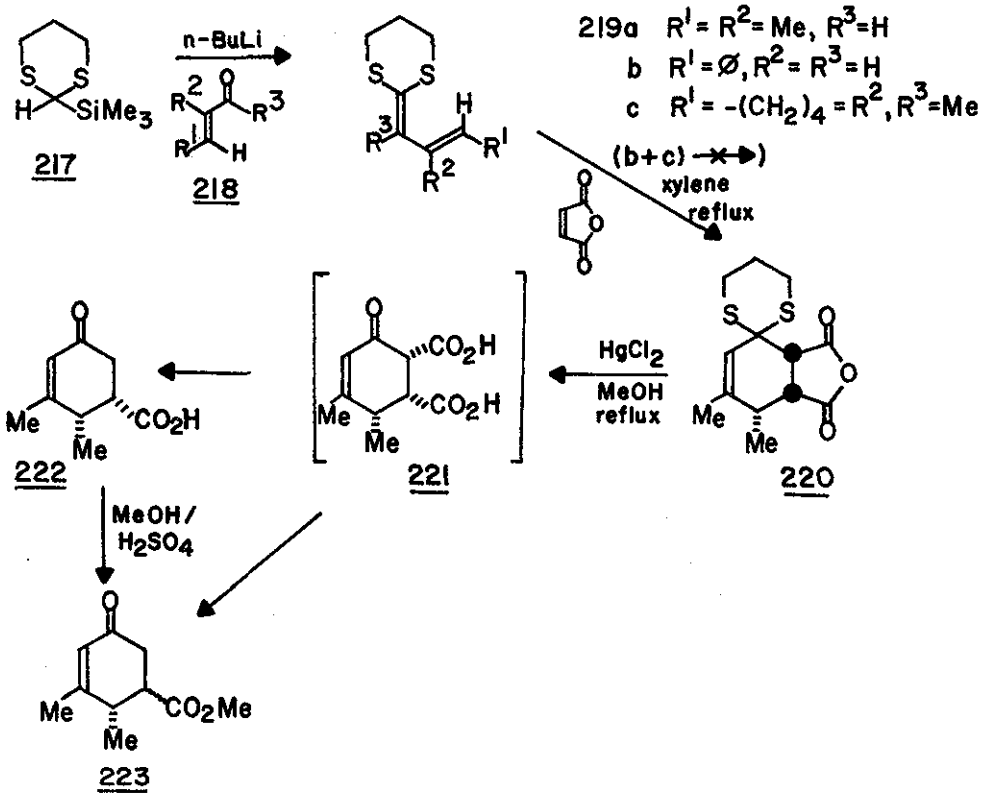
Table 20[75]

Yields of ketene thioacetals 211, and carbonyl compounds employed in their synthesis

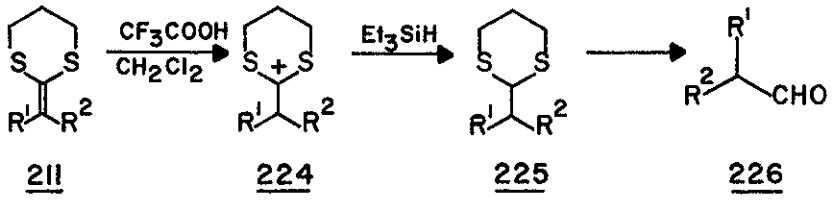
R^1COR^2	% 211
n-PrCHO	67%
i-PrCHO	69
øCH=CHCHO	66
øCHO	68
MeCOMe	45
øCOMe	66
øCOø	75
	69

Using this method, Carey and Court prepared[79] the conjugated alkylidenedithiane 219a, which underwent a Diels-Alder reaction with maleic anhydride to give 220. Once again, this amounts to an alkylation at the 'carbonyl' carbon. Hydrolysis of 220 yielded the keto-acid 222 as well as some of the

methyl ester 223. As a result, the crude mixture was treated with methanol-sulphuric acid, affording pure 223. The yield from 220 was 58% while 219a was transformed to 220 in 60% yield.



Another useful reaction of alkylidene dithianes is their conversion to the saturated dithiane 225. This was achieved by successive treatment of 211 with trifluoroacetic acid in dichloromethane, and triethylsilane[74]. Hydrolysis of 225 then gave the α,α-disubstituted aldehyde 226.



211 224 225 226

The anion 228, generated from ketene thioacetals with n-butyllithium in hexamethylphosphoramide, reacted with alkyl halides to give the olefinic species 229[80]. Hydrolysis with O-mesitylenesulphonylhydroxylamine yielded the α,β-unsaturated ketone 230. Some of the ketones synthesized in this manner are presented in Table 21.

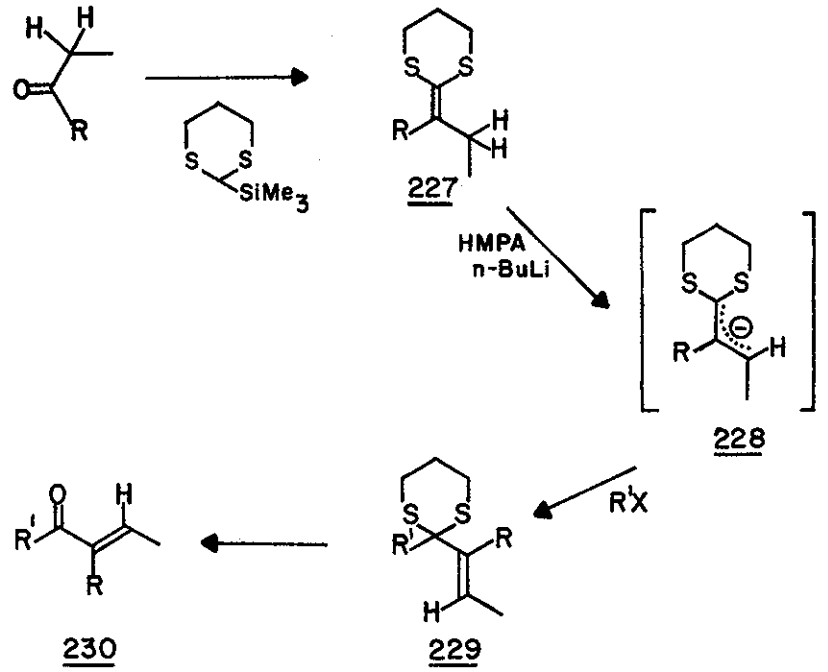
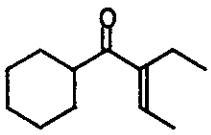
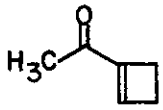
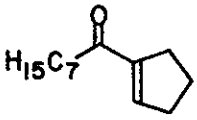
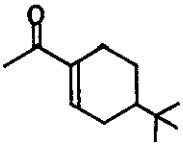
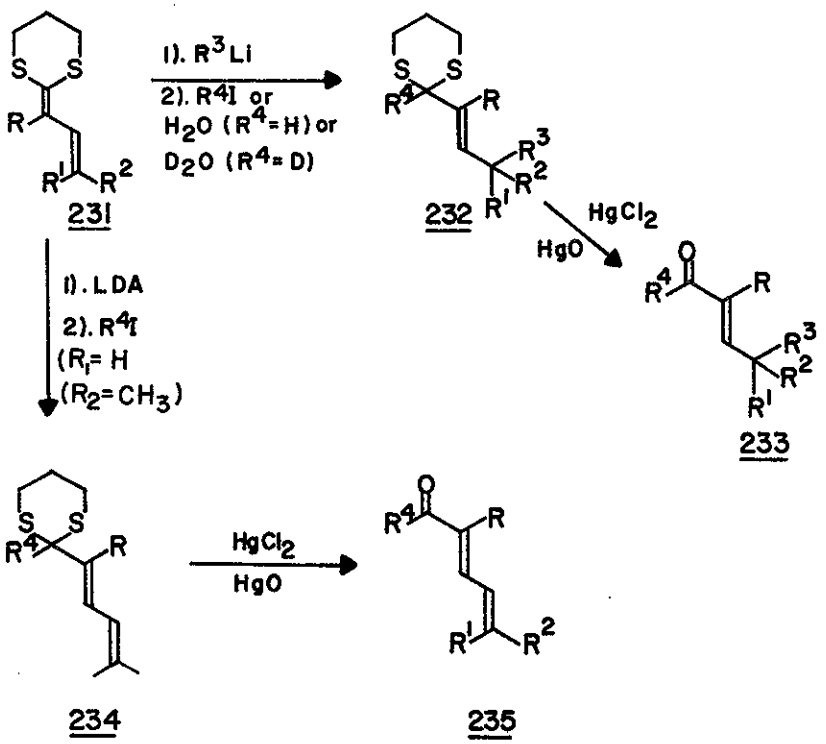


Table 21

α,β-Unsaturated ketones prepared from ketene thioacetals (227)

Ketone	Yield
	51%
	75%
	60%
	65%

A 1,4- or 'Michael' addition to conjugated ketene thioacetals has also been realized by Seebach's group[81]. This amounts to alkylation γ to the masked carbonyl. Hydrolysis of 232, the alkylation product, again yielded an α,β-unsaturated carbonyl compound. When lithium diisopropylamide was used instead of an alkyllithium reagent, proton abstraction occurred and the anion reacted with the alkyl halide as shown (231 → 234).



Meyers' group have prepared the cyano ketene thioacetal 239[82]. Metallation with n-butyllithium and quenching of the resultant anion with an alkyl halide gave mixtures of the products 241 and 242. No further applications of this work have yet been published.

The methoxydithiane 243 reacted with two equivalents of an organolithium reagent to give the anion 245 which was quenched with an alkyl halide[83]. Thus an alkylation was achieved at the 'carbonyl' carbon and α to it. Some results are summarized in Table 22.

Torii et al have published[83a] the results of reactions of dithianes with epoxides. Thus, 2-(2-hydroxy-2,6-dimethyl-5-heptenyl)-1,3-dithiane 248

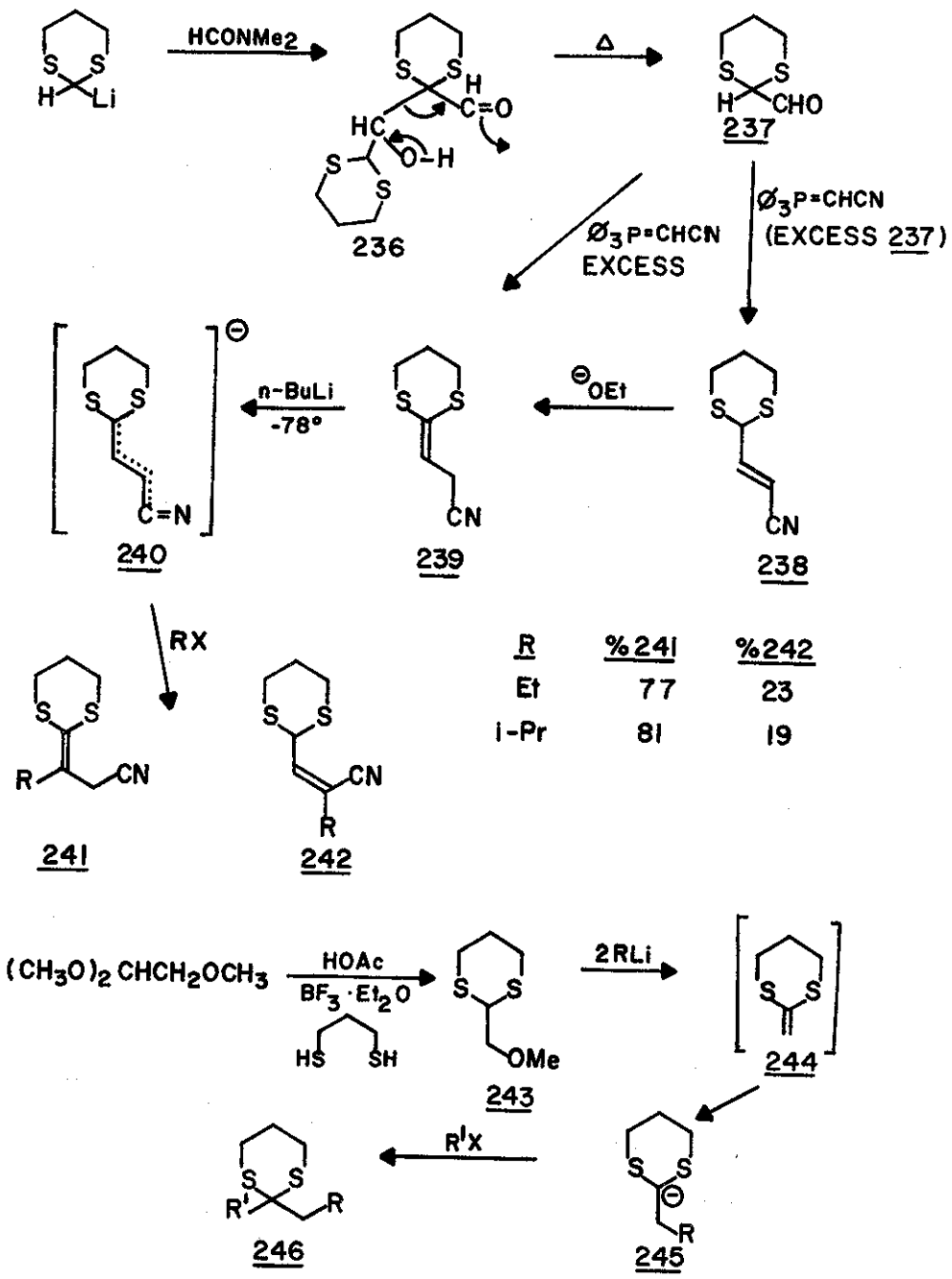
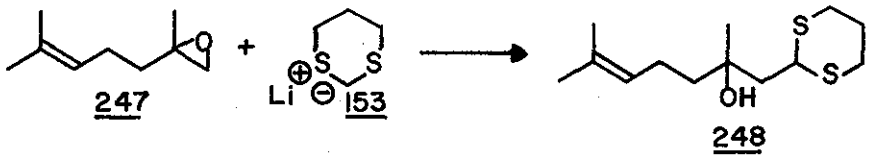

HCONMe2
Δ
236
237
Ø3P=CHCN
EXCESS
Ø3P=CHCN
(EXCESS 237)
n-BuLi
-78°
⊖OEt
240
239
238
RX
241
242
R %241 %242
Et 77 23
i-Pr 81 19
(CH3O)2 CHCH2OCH3
HOAc
BF3·Et2O
2RLi
243
244
R'X
246
245

Table 22

Thioketals prepared from the methoxy-thioacetal 243

R	R^1	% 246 (from 243)
n-Bu	H	91%
sec-Bu	H	94
t-Bu	H	98
n-Bu	n-Am	79

was prepared by reacting 1,2-epoxy-2,6-dimethyl-5-heptene 247 with 2-lithio-1,3-dithiane. Several transformations of 248 were effected, as seen in

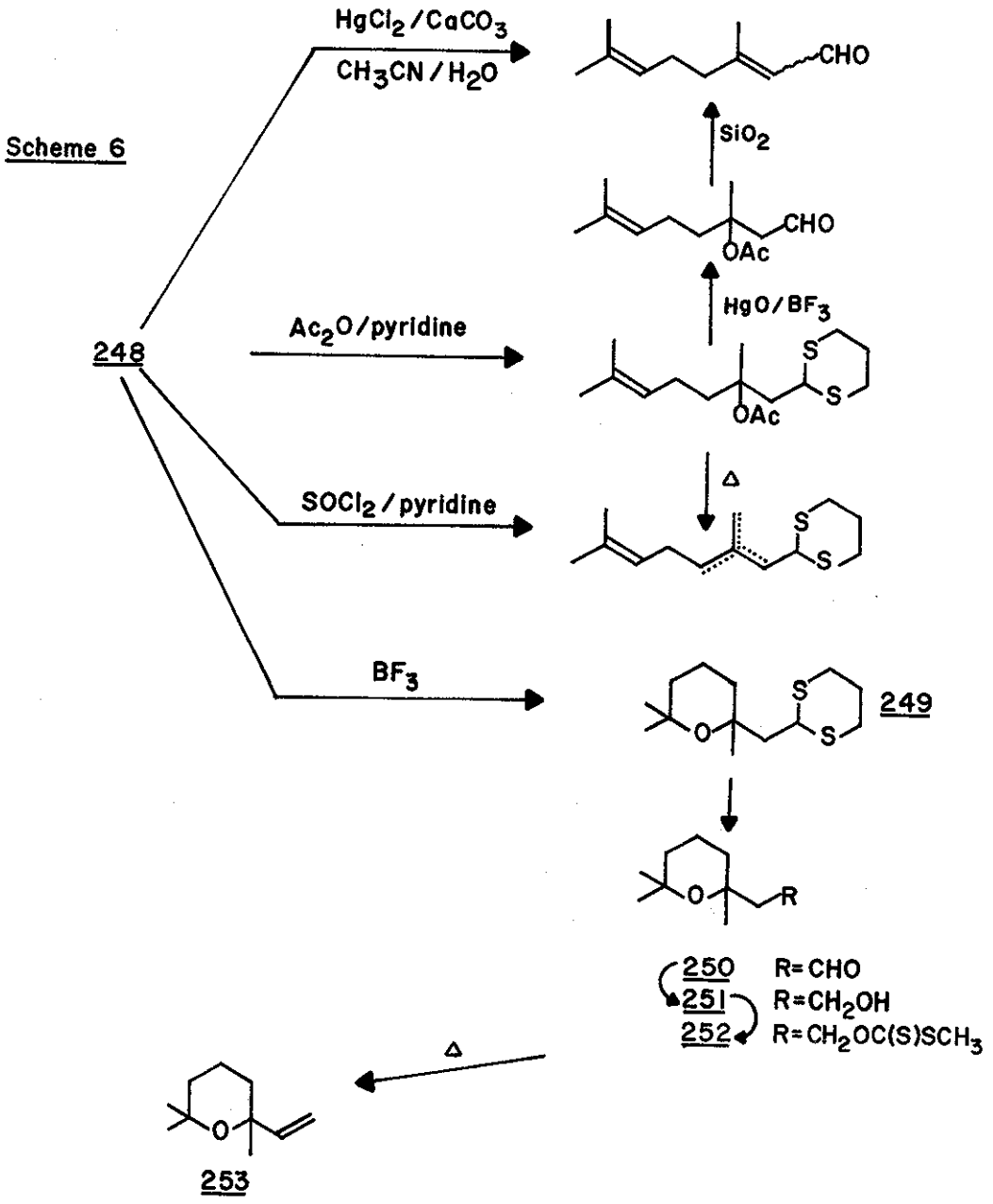


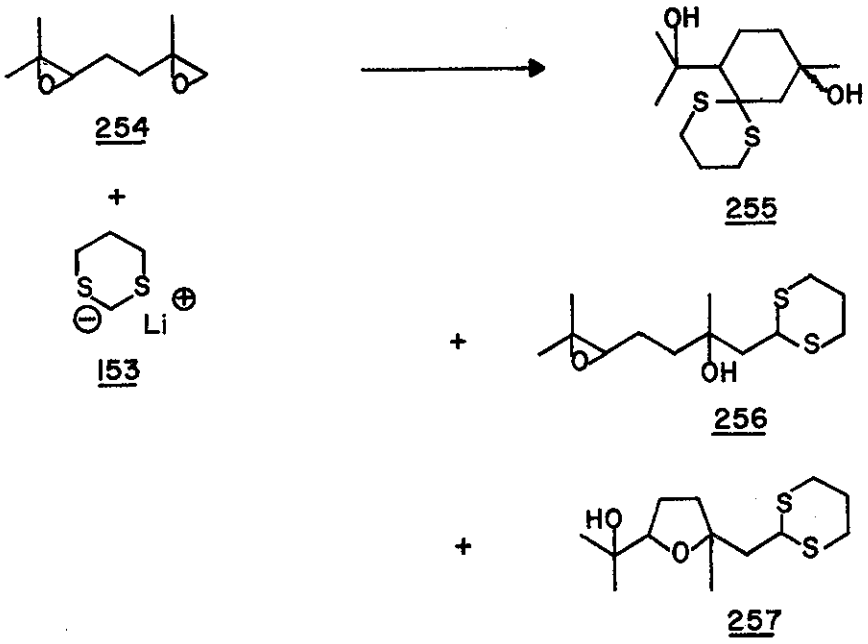
Scheme 6, and it was subsequently converted to linaloyl oxide 253.

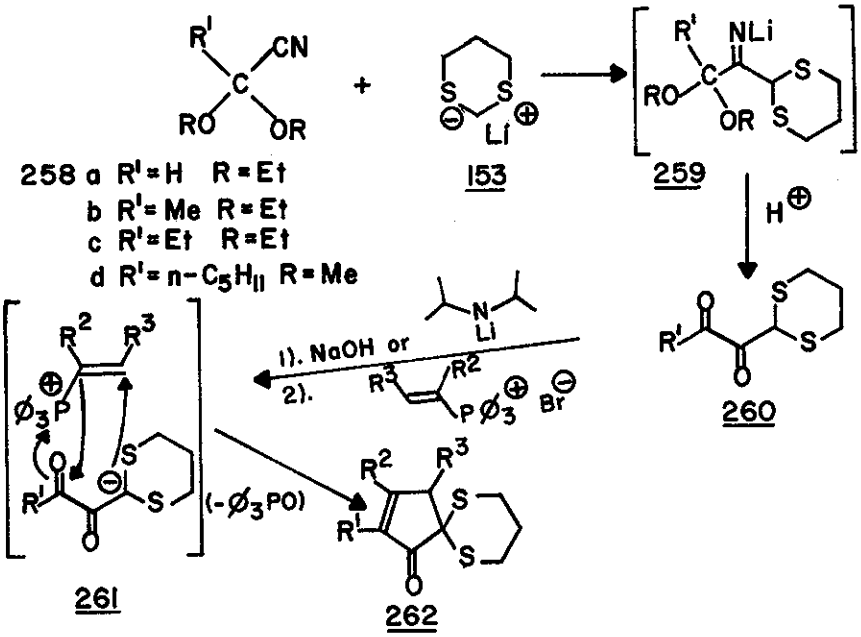
In a prior communication[83b], this group described the reaction of the diepoxide 254 with 153 to give the cyclic compounds 255, 256 and 257.

Dithianes have been employed[83c] in a new synthesis of functionally substituted cyclopentenones. Reaction of 153 with 2,2-dialkoxynitriles 258 gave the intermediate 259 which in turn afforded the α-diketo-dithiane 260 in 50 to 70 percent yield from 258. The cyclopentenone derivatives 262 were prepared by the reaction of vinyl triphenylphosphonium salts with the enolate anion of 260.

Scheme 6

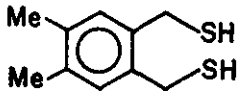

HgCl2 / CaCO3
CH3CN / H2O
CHO
SiO2
CHO
OAc
HgO / BF3
Ac2O / pyridine
248
S
S
OAc
Δ
SOCl2 / pyridine
S
S
BF3
S
249
O
R
250 R=CHO
251 R=CH2OH
252 R=CH2OC(S)SCH3
Δ
O
253


254
255
153
256
257

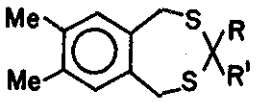

258 a R'=H R=Et
b R'=Me R=Et
c R'=Et R=Et
d R'=n-C5H11 R=Me
153
259
260
261
262
1). NaOH or
2).
(-Ø3PO)

2) 1,3-Dithiepanes

A modification of the dithiane route to carbonyl compounds has utilized derivatives of 1,2-dimethyl-4,5-di(mercaptomethyl)benzene 263. The masked



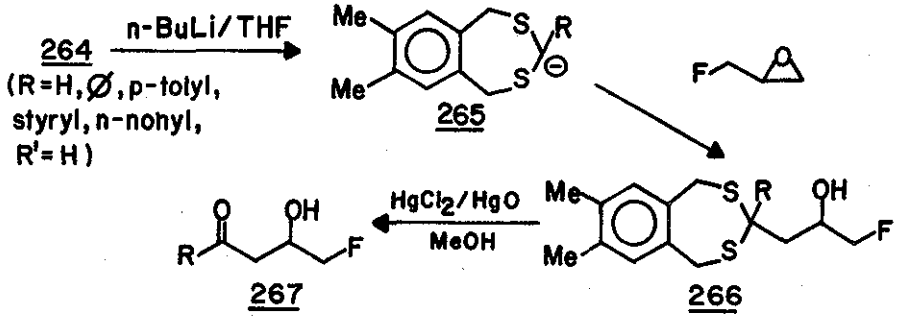
263



264

carbonyl compounds, 264, are readily prepared from 263 and the appropriate aldehyde or ketone[83d]. The above compounds are crystalline and lack the foul smells generally associated with thiols, thioacetals, or thioketals. In this respect, they offer a distinct advantage over the 1,3-dithianes. With regards to reactivity, they behave in an analogous manner to the latter compounds; they are stable to hot aqueous solutions of acids and bases, Grignard reagents, and reducing agents of the borohydride type, they can be cleaved with mercuric salts to regenerate the carbonyl moiety, and they can be metallated[83e] with n-butyllithium in order to effect alkylation at the carbon of the masked carbonyl.

Fluorinated keto alcohols 267, isolated as their DNP derivatives, were prepared[83e] by treatment of the anion of 264 with a small excess of 1,2-epoxy-3-fluoropropane and subsequent cleavage of the thioacetal or thioketal produced with mercuric chloride-mercuric oxide in methanol. Overall yields ranged from 6 to 43 percent.



Mori and his co-workers have reacted the lithiated species 265 (R=H, Me) with various alkyl halides to give compounds typified by 264[83f]. Their results are presented in Table 23. Cleavage to the corresponding aldehyde or ketone was effected with cupric oxide-cupric chloride[54].

Table 23

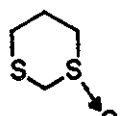
Results of 1,3-dithiepane alkylation

Alkylating Agent	Starting Material	Product	Yield
$n\text{-}C_4H_9Br$	264 R=R'=H	264 R'=$n\text{-}C_4H_9$,R=H	92%
	R=Me,R'=H	R'=$n\text{-}C_4H_9$,R=Me	85
$H_2C{=}CHCH_2Br$	264 R=R'=H	264 R'=$H_2C{=}CHCH_2$,R=H	91
	R=Me,R'=H	R'=$H_2C{=}CHCH_2$,R=Me	79
ϕCH_2Br	264 R=R'=H	264 R'=ϕCH_2,R=H	71
	R=Me,R'=H	R'=ϕCH_2,R=Me	50
$Me_2{=}CH(CH_2)_2Br$	264 R=R'=H	264 R'= $Me_2{=}CH(CH_2)_2$,R=H	75
	R=Me,R'=H	R'= $Me_2{=}CH(CH_2)_2$,R=Me	61
$n\text{-}C_{10}H_{21}Br$	264 R=R'=H	264 R'=$n\text{-}C_{10}H_{21}$,R=H	74
	R=Me,R'=H	R'=$n\text{-}C_{10}H_{21}$,R=Me	88

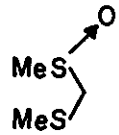
3) Thioacetal Monosulphoxides

Recently, Schlessinger's group have developed procedures by which carbonyl compounds can be prepared from thioacetal monosulphoxides. Although not cyclic compounds, they will be discussed here as they were introduced as a versatile alternative to the dithiane system.

In searching for an unsymmetrical sulphur system that could be alkylated by α,β-unsaturated carbonyl systems as well as alkyl halides, Schlessinger examined the previously reported sulphoxides 268[84] and 269,[85] which were said to react with electrophiles, but he could not reproduce the reported results satisfactorily[86]. However, the diethyl analogue of 269 gave the anion 271

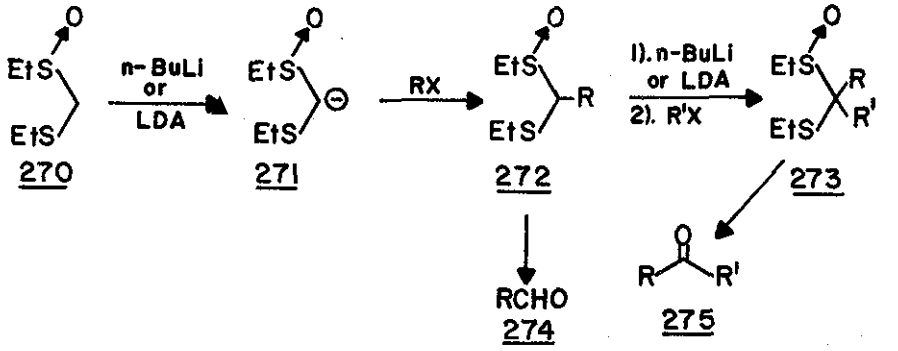


268



269

quantitatively in less than thirty minutes when treated with n-butyllithium or lithium diisopropylamide at 2°, and it could be monoalkylated in greater than 95% yield. A second alkylation could be accomplished using the same conditions; this time in better than 90% yield. Hydrolysis of 272

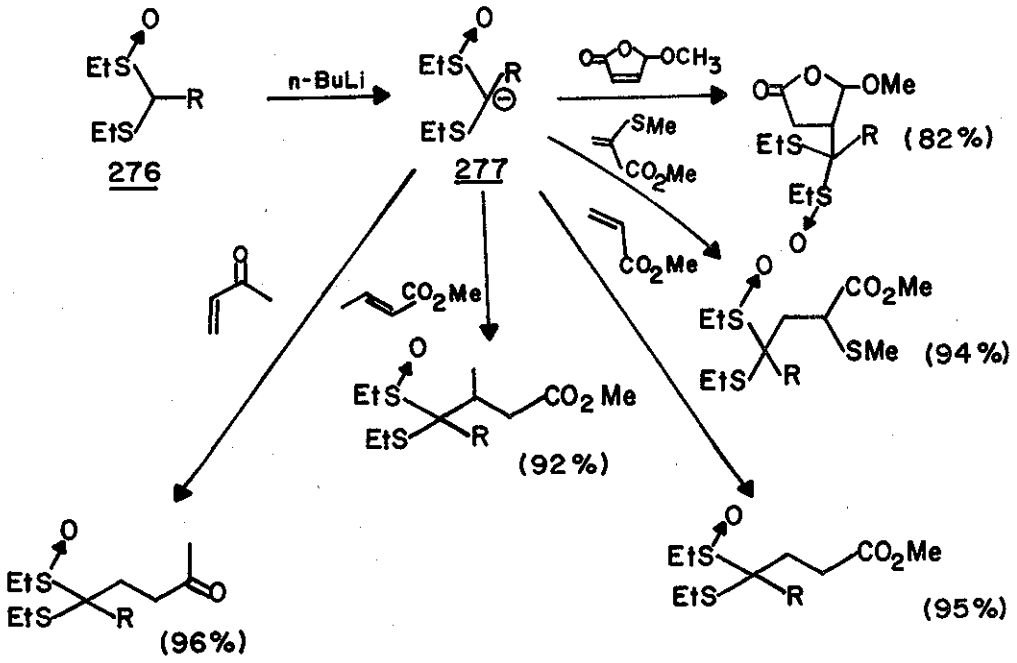


or 273 gave the corresponding aldehyde or ketone. The deblocking was performed in quantitative yield with a catalytic amount of 70% perchloric acid, but there was a problem of contamination with ethyl disulphide. This presented difficulties with aldehydes or ketones having a boiling point of less than 220° at one torr, but could be avoided by hydrolyzing the thioacetal monosulphoxide in the presence of a mercuric salt. Four equivalents of mercuric chloride in a 4:1 mixture of tetrahydrofuran and 9N hydrochloric acid was found to be the optimum 'reagent', giving the deblocked compound in 80-95% yield.

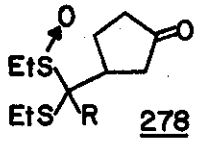
The thioacetal monosulphoxide 270 was prepared by reacting formaldehyde with ethyl mercaptan and oxidizing the thioacetal produced with metaperiodate.

Schlessinger also found that the anion 277 would add in a 1,4-fashion to α,β-unsaturated carbonyl compounds[87]. Yields with a variety of functional group types were uniformly in the 80 to 95% range, providing an excellent synthesis of 1,4-dicarbonyl systems. Typical results are depicted in Scheme 7. Two equivalents of cyclopentenone were required to produce a 70% yield (based on the thioacetal 276) of the adduct 278, and cyclohexenone and its derivatives gave only moderate yields.

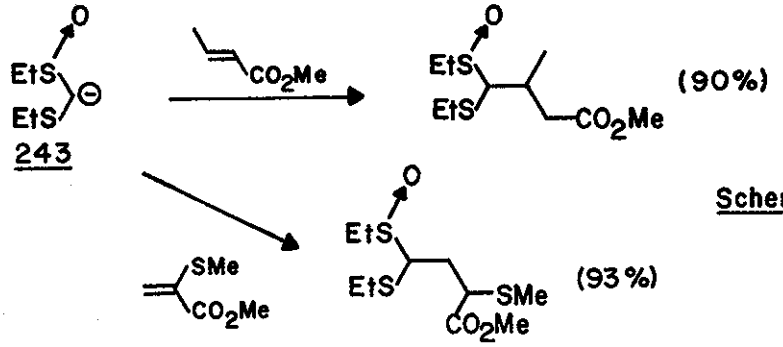
The unsubstituted anion 271 was also found to undergo conjugate addition



Scheme 7



with α,β-unsaturated esters (Scheme 8), but added to the carbonyl moiety of unsaturated ketones. The latter characteristic was later developed by this

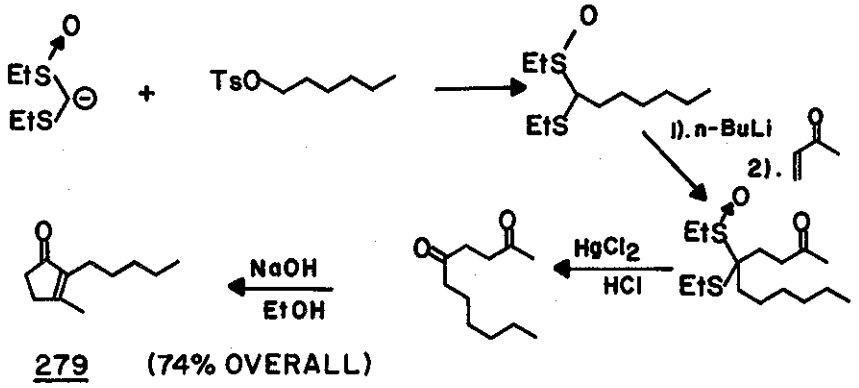


Scheme 8

group as a means of acylating thioacetals[88] and will be discussed subsequently.

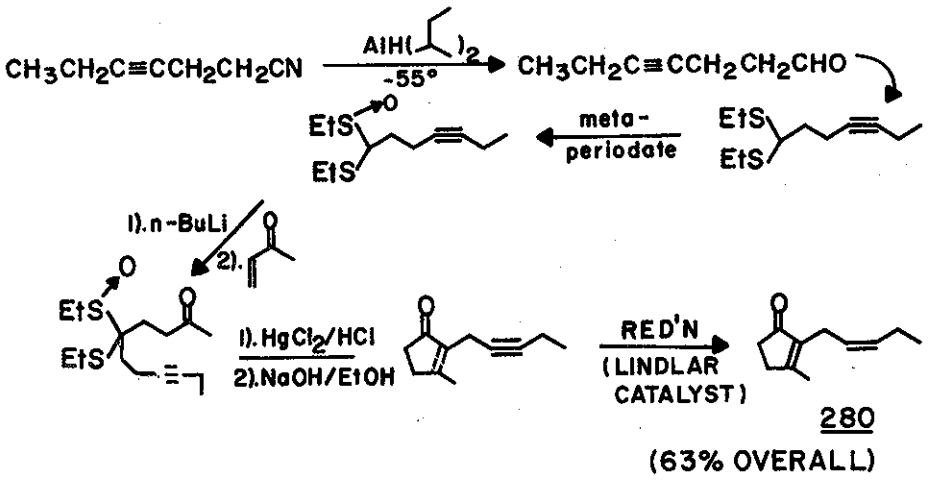
The ease with which the thioacetal derivatives condensed with unsaturated carbonyl systems leading ultimately to 1,4-dicarbonyl structures, was exploited by Schlessinger et al.[89] in high yield syntheses of dihydrojasmone 279 and cis-jasmone 280. These routes are presented in Schemes 9 and 10.

Scheme 9



279 (74% OVERALL)

Scheme 10



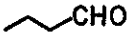
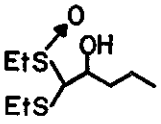
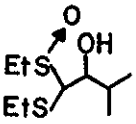
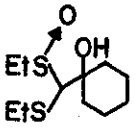
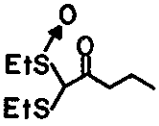
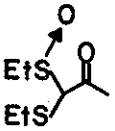
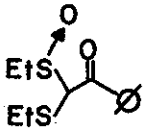
280

(63% OVERALL)

The anion 271 undergoes smooth 1,2-addition to aldehydes, ketones, esters, and acid chlorides[88]. The latter two types of compounds require two equivalents of the anion, whereas aldehydes and ketones react on a 1:1 basis. Some typical results are presented in the following table:

Table 24

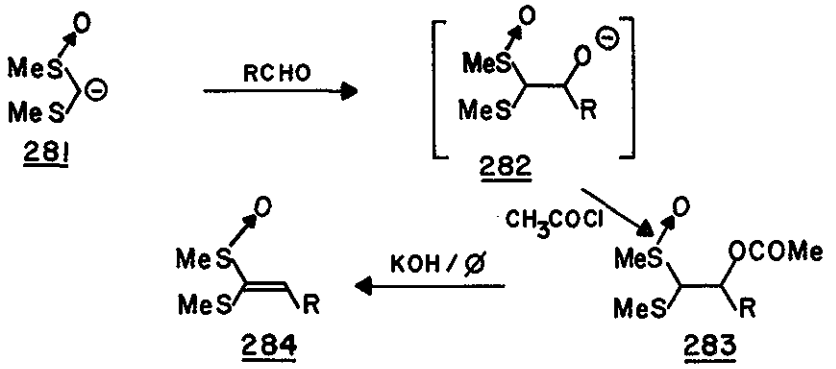
Products from the condensation of aldehydes, ketones, esters, and acid chlorides with the thioacetal monosulphoxide anion 271

Carbonyl Compound	Adduct	Yield
		95%
		97
		96
		90
CH_3COCl		92
$\varnothing COCl$		90

After hydrolysis, α-functionalized or α,β-unsaturated carbonyl compounds result.

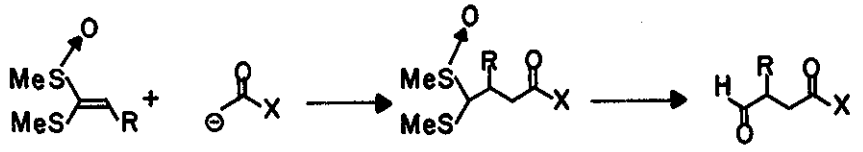
For substituted analogues of the anion, the reaction still proceeds in high yield with aldehydes and acid chlorides, but esters and ketones react only sluggishly.

Reaction of 281 with an aldehyde yielded the anion 282, which was quenched with acetyl chloride, forming the ester 283[88]. On refluxing this compound in potassium hydroxide-benzene, elimination to the ketene thioacetal monosulphoxide 284 occurred. These compounds were used as 2-carbon Michael receptors[90], resulting in the equivalent of alkylation α to a carbonyl and



ultimately producing 1,4-dicarbonyl systems. The generalized reaction is shown in Scheme 11. This Michael addition was effective with three classes

Scheme II

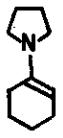
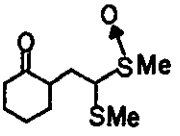
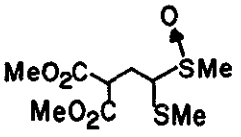
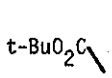
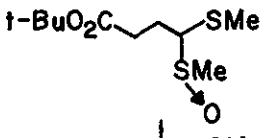
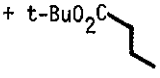
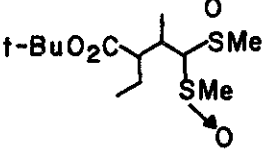


of compounds: enamines, sodium enolates derived from β-dicarbonyl compounds (or other compounds capable of generating a doubly stabilized anion), and

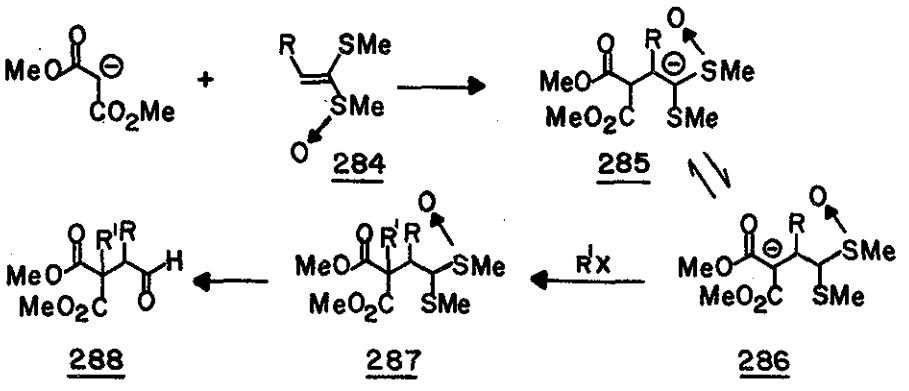
lithium enolates derived from simple ester systems. Some examples and the corresponding yields can be found in Table 25.

Table 25

Products from the Michael addition of various anionic species to the ketene thioacetal 284

Reactants	Product	Yield
284, R=H + 		92%
284, R=H + 		98
284, R=H + 		94
284, R=Me + 		90

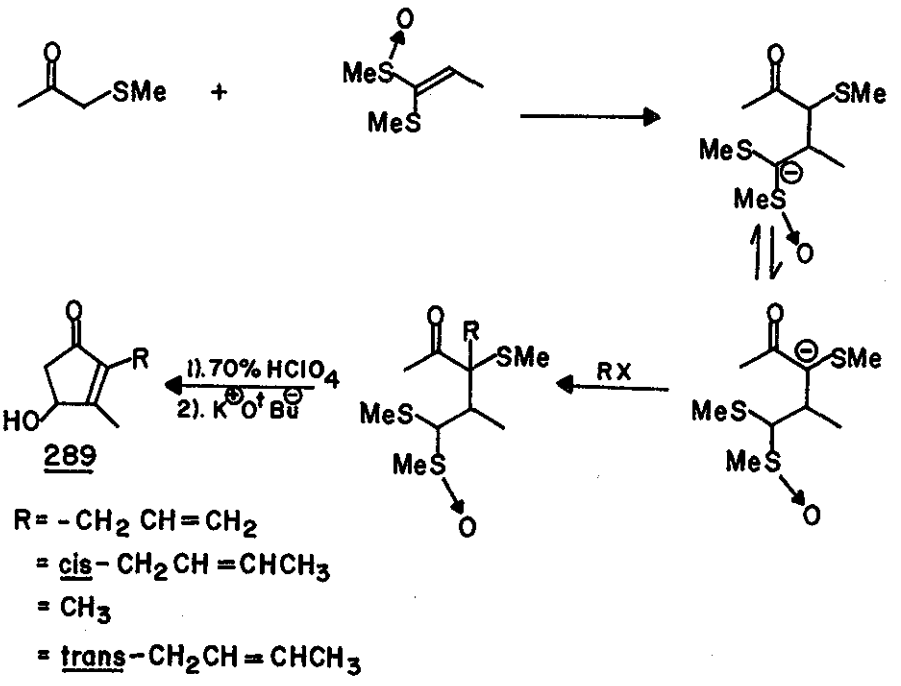
In the case of the reaction between 284 and β-dicarbonyl systems, the anion 285 was formed and then was equilibrated to 286[91]. Addition of an



alkyl halide to this anion led to the thioacetal monosulphoxide 287, a precursor to unsymmetrical 1,4-dicarbonyl compounds.

This technique was applied to the synthesis of rethrolones (289)[92] and proved to be an efficient method giving uniformly high yields (Scheme 12).

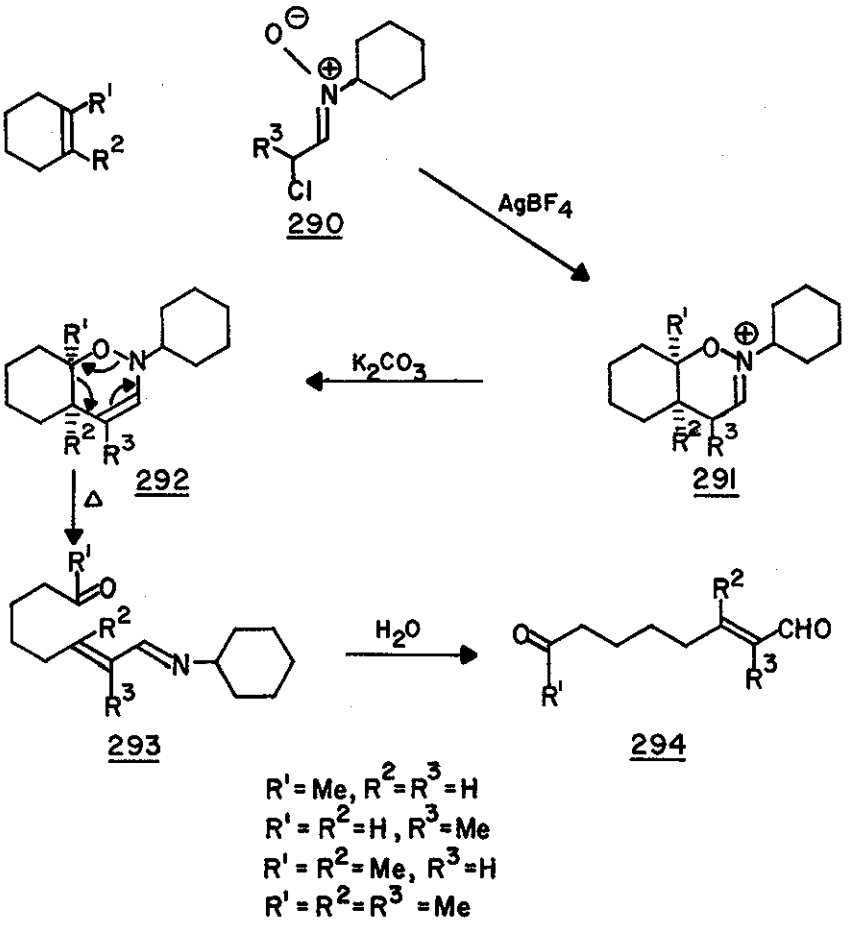
Scheme 12



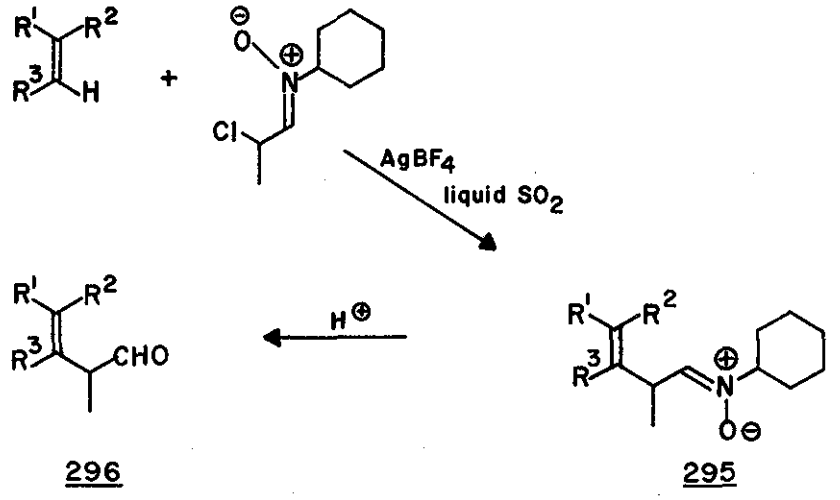
4) 1,2-Isoxazines

Olefins and α-chloronitrones 290 undergo a cycloaddition reaction in the presence of silver tetrafluoroborate, affording isoxazinium salts 291 in high yield[93,94]. Neutralization with potassium carbonate produces the isoxazine 292 which rearranges to the imine 293, when heated. Finally, an α,β-unsaturated aldehyde results from hydrolysis of this compound. The net result is alkylation α to a carbonyl and formation of a trisubstituted

olefin, the latter often a difficult objective in a synthetic program.



When unsymmetric di- and trisubstituted olefins, or nucleophilic aromatic nuclei, were reacted with 290 (R^3=Me) in liquid sulphur dioxide, a novel substitution was observed[95] rather than a cycloaddition process, affording 295. The β,γ-unsaturated aldehyde 296 was isolated by acid treatment of 295.



296 295

When the α-chloronitrone 290 was added to silver tetrafluoroborate in sulphur dioxide in the presence of an acetylenic compound, followed by basic alumina treatment, an α,β-unsaturated ketone 300 was obtained[96] in 70 to 80 percent yield, presumably via the cyclic species 298 and 299.

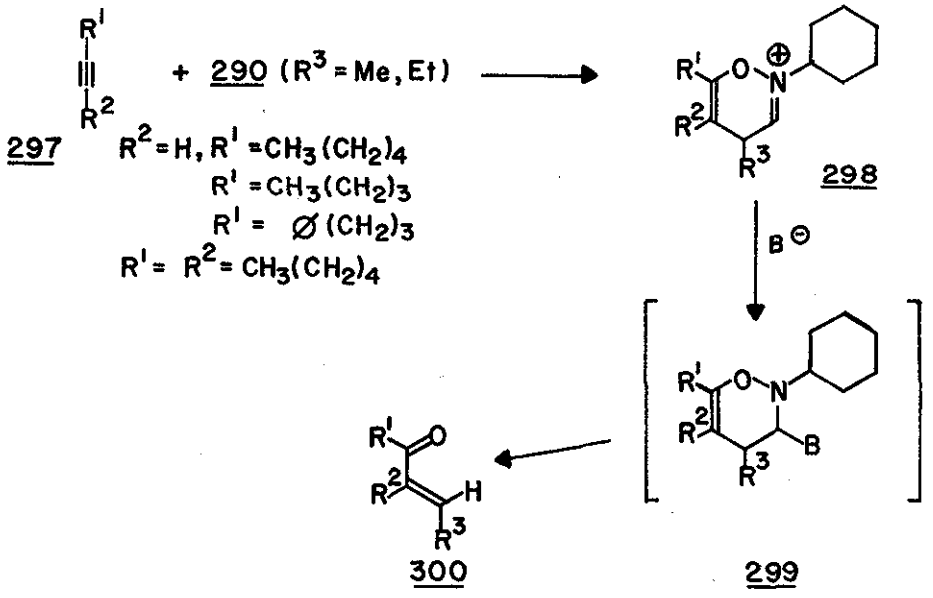
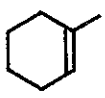
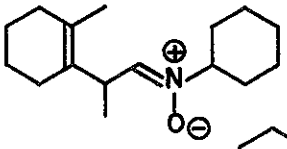
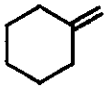
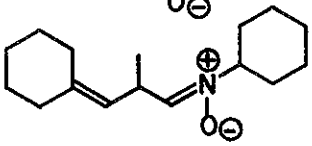
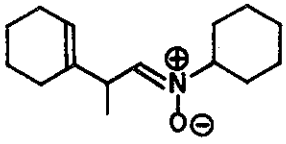
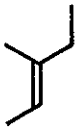
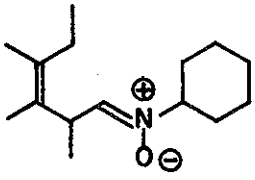
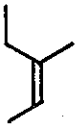
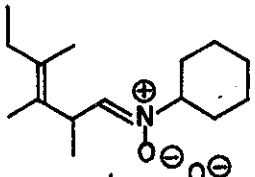
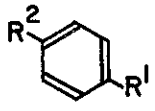
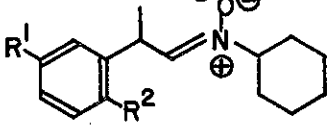


Table 26

Substitution products (295) of α-chloronitrones and olefins

Olefin	Product (295)	Yield 295	Cycloaddition Product
		59%	
		60%	
		14%	82%
		50%	30%
		55%	35%
		~80% (in all cases)	

$R^1 = OMe, R^2 = OMe, Me$

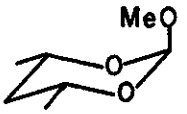
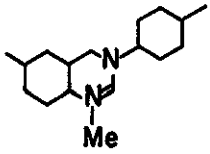
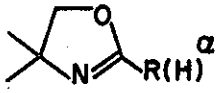
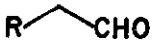
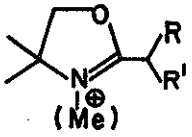
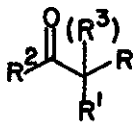
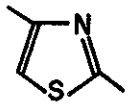
$R^1 = R^2 = Me$

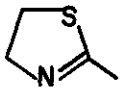
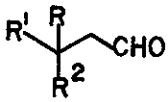
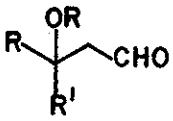
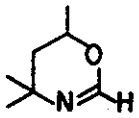
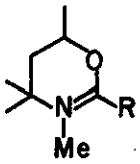
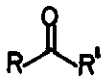
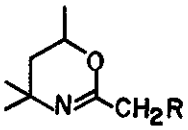
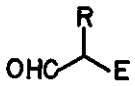
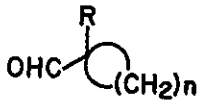
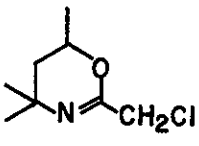
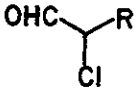
Summary

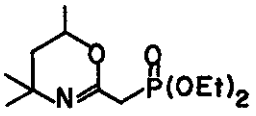
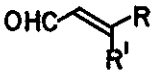
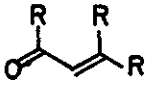
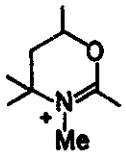
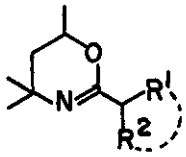
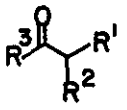
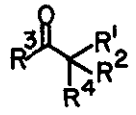
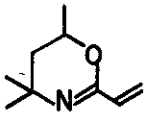
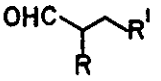
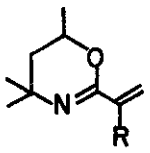
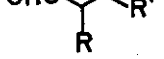
Rather than try to summarize in words the variety of carbonyl compounds available via the eleven heterocycles considered, the general structural features available from each one are presented in a table:

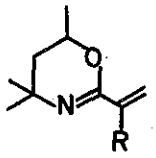
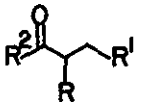
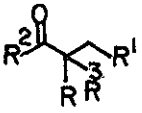
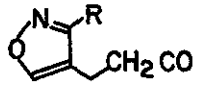
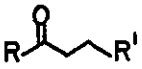
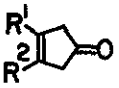
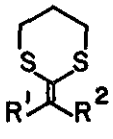
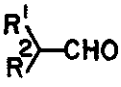
Table 27

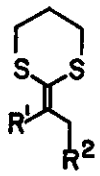
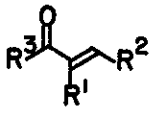
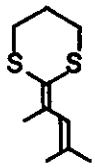
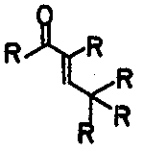
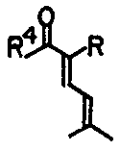
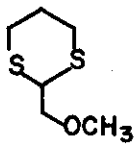
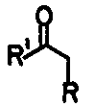
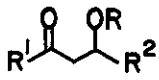
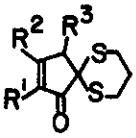
Structural features of carbonyl compounds available from the heterocyclic compounds discussed

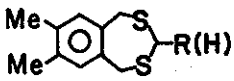
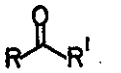
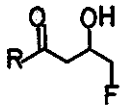
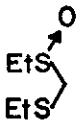
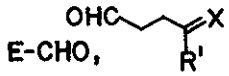
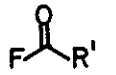
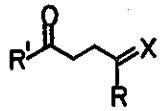
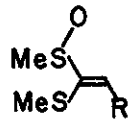
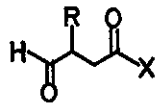
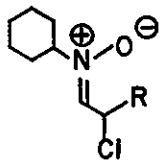
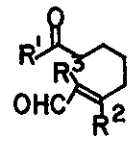
Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	CARBONYL		RCHO	$H^{\oplus}$
	CARBONYL		RCHO	$H^{\oplus}$
	α (CARBONYL)			$H^{\oplus}$
	CARBONYL	(α)		$H^{\oplus}$
	α			NEUTRAL

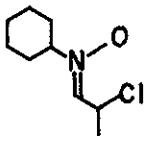
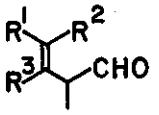
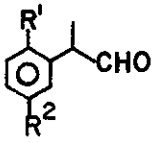
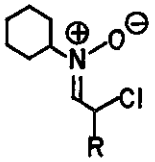
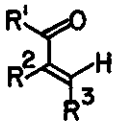
Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	α			NEUTRAL
	α			NEUTRAL
	CARBONYL		RCHO	$H^{\oplus}$
	CARBONYL			$H^{\oplus}$
	α			$H^{\oplus}$
	α			$H^{\oplus}$
	α			$H^{\oplus}$

Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	α			$H^{\oplus}$
	α	CARBONYL		$H^{\oplus}$
	α		$OHCCH_2R$	$H^{\oplus}$
	CARBONYL			$H^{\oplus}$
	CARBONYL	α		$H^{\oplus}$
	β	α		$H^{\oplus}$
	β			$H^{\oplus}$

Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	β	CARBONYL		$H^{\oplus}$
	β α	CARBONYL		$H^{\oplus}$
	β			$[H]\,/\,\overset{\ominus}{O}H$
	CARBONYL		ECHO	NEUTRAL, $H^{\oplus}$
	CARBONYL			NEUTRAL, $H^{\oplus}$
	CARBONYL			NEUTRAL, $H^{\oplus}$
				NEUTRAL, $H^{\oplus}$

Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	CARBONYL			NEUTRAL, $H^{\oplus}$
	γ	CARBONYL		NEUTRAL, $H^{\oplus}$
	CARBONYL			NEUTRAL, $H^{\oplus}$
	α	CARBONYL		NEUTRAL, $H^{\oplus}$
	CARBONYL			NEUTRAL
	CARBONYL			

Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	CARBONYL			NEUTRAL
				NEUTRAL
	CARBONYL			$H^{\oplus}$
	CARBONYL			$H^{\oplus}$
	CARBONYL			$H^{\oplus}$
	α			$H^{\oplus}$
	α			NEUTRAL

Heterocycle	Alkylation Position	Other Positions	Product	Demasking Conditions
	α			$H^{\oplus}$
				$H^{\oplus}$
	(REARRANGEMENT)			$B^{\ominus}$

Acknowledgements

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References

1) E. L. Eliel and F. W. Nader, J. Amer. Chem. Soc., 92, 584 (1970).
2) H. M. Fales, ibid., 77, 5118 (1955).
3) For a review of the synthetic applications of 2-oxazolines and dihydro-1,3-oxazines, see: E. W. Collington, Chem. Ind., 987 (1973).
4) A. I. Meyers and E. W. Collington, J. Amer. Chem. Soc., 92, 6676 (1970).
5) P. Allen Jr. and J. Ginos, J. Org. Chem., 28, 2759 (1963).
6) I. C. Nordin, J. Heterocycl. Chem., 3, 531 (1966).
7) C. Lion and J. E. Dubois, Tetrahedron, 29, 3417 (1973).
8) C. Lion and J. E. Dubois, Bull. Soc. Chim. (Fr.), 2673 (1973).
9) A. I. Meyers and D. L. Temple Jr., J. Amer. Chem. Soc., 92, 6644, 6646 (1970).
10) L. F. Altman and S. L. Richheimer, Tetrahedron Lett., 4709 (1971).
11) A. I. Meyers and G. N. Knaus, J. Amer. Chem. Soc., 95, 3408 (1973).
12) G. Knaus and A. I. Meyers, J. Org. Chem., 39, 1189 (1974).
13) Ibid., 39, 1192 (1974).
14) A. I. Meyers, R. Munavu and J. Durandetta, Tetrahedron Lett., 3929 (1972).
14a A. I. Meyers and J. L. Durandetta, J. Org. Chem., 40, 2021 (1975).
15) A. I. Meyers, "Heterocycles in Organic Synthesis", General Heterocyclic Chemistry Series, Vol. 3, E. C. Taylor and A. Weissberger, ed., Wiley-Interscience, 1974, pp. 211-212.
15a A. I. Meyers, J. L. Durandetta and R. Munavu, J. Org. Chem., 40, 2025 (1975).
16) E.-J. Tillmanns and J. J. Ritter, ibid., 22, 839 (1957).
17) Z. Eckstein and T. Urbanski, Adv. Heterocycl. Chem., 2, 311 (1963).
18) R. R. Schmidt, Chem. Ber., 103, 3242 (1970).
19) A. I. Meyers, A. Nabeya, H. W. Adickes, J. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, J. Org. Chem., 38, 36 (1973).
20) A. I. Meyers and H. W. Adickes, Tetrahedron Lett., 5151 (1969).
21) A. I. Meyers and E. M. Smith, J. Amer. Chem. Soc., 92, 1084 (1970).
22) A. I. Meyers and E. M. Smith, J. Org. Chem., 37, 4289 (1972).
23) A. I. Meyers and N. Nazarenko, ibid., 38, 175 (1973).
24) J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, H. W. Adickes and A. I. Meyers, Org. Prep. Proc., 1 193 (1969).

25) A. I. Meyers, A. Nabeya, H. W. Adickes and I. R. Politzer, J. Amer. Chem. Soc., 91, 763 (1969).
26) A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Politzer, ibid., 91, 764 (1969).
27) H. W. Adickes, I. R. Politzer and A. I. Meyers, ibid., 91, 2155 (1969).
28) A. I. Meyers, H. W. Adickes, I. R. Politzer and W. N. Beverung, ibid., 91, 765 (1969).
29) G. R. Malone and A. I. Meyers, J. Org. Chem., 39, 618 (1974).
30) Ibid., 39, 623 (1974).
31) W. S. Wadsworth and W. D. Emmons, J. Amer. Chem. Soc., 83, 1733 (1961).
32) A. I. Meyers and N. Nazarenko, ibid., 94, 3243 (1972).
33) A. I. Meyers, E. M. Smith and A. F. Jurjevich, ibid., 93, 2314 (1971).
34) A. I. Meyers, E. M. Smith and M. S. Ao, J. Org. Chem., 38, 2129 (1973).
35) G. Stork and S. Dowd, J. Amer. Chem. Soc., 85, 2178 (1963).
36) A. I. Meyers and A. C. Kovelesky, Tetrahedron Lett., 1783 (1969).
37) A. C. Kovelesky and A. I. Meyers, Org. Prep. Proc., 1, 213 (1969).
38) A. I. Meyers and A. C. Kovelesky, Tetrahedron Lett., 4809 (1969).
39) A. I. Meyers and A. C. Kovelesky, J. Amer. Chem. Soc., 91, 5887 (1969).
40) A. I. Meyers, A. C. Kovelesky and A. F. Jurjevich, J. Org. Chem., 38, 2136 (1973).
41) G. Stork and J. E. McMurry, J. Amer. Chem. Soc., 89 5464 (1967).
42) J. W. Scott and G. Saucy, J. Org. Chem., 37, 1652 (1972).
43) J. W. Scott, R. Boter and G. Saucy, ibid., 37, 1659 (1972).
44) N. K. Kochetkov and S. D. Sokolov, Adv. Heterocycl. Chem., 2, 365 (1963).
45) G. Stork, S. Danishefsky and M. Ohashi, J. Amer. Chem. Soc., 89, 5459 (1967).
46) G. Stork and J. E. McMurry, ibid., 89, 5461 (1967).
47) T. Tanaka, M. Miyazaki and I. Iijima, Chem. Commun., 233 (1973).
48) S. Auricchio and A. Ricca, Gazz. Chim. Ital., 103, 37 (1973).
49) E. J. Corey and D. Seebach, Angew. Chem. Int. Ed., 4, 1075, 1077 (1965).
50) D. Seebach, Synthesis, 17 (1969) and references cited therein.
50a D. Seebach and E. J. Corey, J. Org. Chem., 40, 231 (1975).
51) D. Seebach, N. R. Jones and E. J. Corey, ibid., 33, 300 (1968).
52) E. J. Corey and B. W. Erickson, J. Org. Chem., 36, 3553 (1971).
53) E. Vedejs and P. L. Fuchs, ibid., 36, 366 (1971).
54) K. Narasaka, T. Sakashita and T. Mukaiyama, Bull. Chem. Soc. Japan, 45, 3724 (1972).

55) M. Fetizon and M. Jurion, Chem. Commun., 382 (1972).
56) T.-L. Ho, H. C. Ho and C. M. Wong, ibid., 791 (1972).
57) T.-L. Ho and C. M. Wong, Can. J. Chem., 50, 3740 (1972).
58) T.-L. Ho and C. M. Wong, Synthesis, 561 (1972).
59) T.-L. Ho, H. C. Ho and C. M. Wong, Can. J. Chem., 51, 153 (1973).
60) Y. Tamura, K. Sumoto, S. Fujii, H. Satoh and M. Ikeda, Synthesis, 312 (1973).
61) D. Seebach, B. W. Erickson, G. Singh, J. Org. Chem., 31, 4303 (1966).
62) D. Seebach and D. Steinmuller, Angew. Chem., 80, 617 (1968).
63) D. Seebach, D. Steinmuller and F. Demuth, ibid., 80, 618 (1968).
64) E. J. Corey et al., J. Amer. Chem. Soc., 90, 3245 (1968).
65) T. Hylton and V. Boekelheide, ibid., 90, 6887 (1968).
66) E. J. Corey and D. Crouse, J. Org. Chem., 33, 298 (1968).
67) E. J. Corey, D. Seebach, R. Freedman, J. Amer. Chem. Soc., 89, 434 (1967).
68) W. D. Woessner and R. A. Allison, Tetrahedron Lett., 3735 (1972).
69) E. J. Corey and S. W. Walinsky, J. Amer. Chem. Soc., 94, 8932 (1972).
70) E. W. Colvin, T. A. Purcell and R. A. Raphael, Chem. Commun., 1081 (1972).
71) D. Seebach and H. F. Leitz, Angew. Chem. Int. Ed., 10, 983 (1969).
72) E. J. Corey and G. Markl, Tetrahedron Lett., 3201 (1967).
73) J. A. Marshall and J. A. Belletire, ibid., 871 (1971).
74) F. A. Carey and A. S. Court, J. Org. Chem., 37, 1926 (1972).
75) P. F. Jones and M. F. Lappert, Chem. Commun., 526 (1972).
76) P. F. Jones, M. F. Lappert and A. C. Szary, J. C. S. Perkin I, 2272 (1973).
77) D. Seebach, B.-Th. Grobel, A. K. Beck, M. Braun and K.-H. Geiss, Angew. Chem. Int. Ed., 11, 443 (1972).
78) D. Seebach, M. Kolb and B.-Th. Grobel, Chem. Ber., 106, 2277 (1973).
79) F. A. Carey and A. S. Court, J. Org. Chem., 37, 4474 (1972).
80) D. Seebach, M. Kolb and B.-Th. Grobel, Tetrahedron Lett., 3171 (1974).
81) D. Seebach, M. Kolb and B.-Th. Grobel, Angew. Chem. Int. Ed., 12, 69 (1973).
82) A. I. Meyers and R. C. Strickland, J. Org. Chem., 37, 2579 (1972).
83) R. M. Carlson and P. M. Helquist, Tetrahedron Lett., 173 (1969).
83a S. Torii, K. Uneyama and M. Isihara, J. Org. Chem., 39, 3645 (1974).

83b S. Torii, Y. Matuyama, M. Isihara and K. Uneyama, Chem. Lett., 947 (1973).
83c I. Kawamoto, S. Muramatsu and Y. Yura, Tetrahedron Lett., 4223 (1974).
83d I. Shakak and E. D. Bergmann, J. Chem. Soc., (C), 1005 (1966).
83e S. Rozen, I. Shahak and E. D. Bergmann, Tetrahedron Lett., 1837 (1972).
83f K. Mori, H. Hashimoto, Y. Takenaka and T. Takigawa, Synthesis, 720 (1975).
84) R. M.Carlson and P. M. Helquist, J. Org. Chem., 33, 2596 (1968).
85) K. Ogura and G. Tsuchihashi, Tetrahedron Lett., 3151 (1971).
86) J. E. Richman, J. L. Herrmann and R. H. Schlessinger, ibid., 3267 (1973).
87) Ibid., 3271 (1973).
88) J. L. Herrmann,J. E. Richman, P. J. Wepplo and R. H. Schlessinger, ibid., 4707 (1973).
89) J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, ibid., 3275 (1973).
90) J. L. Herrmann, G. R. Kieczykowski, R. F. Romanet, P. J. Wepplo and R. H. Schlessinger, ibid., 4711 (1973).
91) J. L. Herrmann,G. R. Kieczykowski, R. F. Romanet and R. H. Schlessinger, ibid., 4715 (1973).
92) R. F. Romanet and R. H. Schlessinger, J. Amer. Chem. Soc., 96, 3701 (1974).
93) U. M. Kempe, T. K. Das Gupta, K. Blatt, P. Gygax, D. Felix and A. Eschenmoser, Helv. Chim. Acta, 55, 2187 (1972).
94) P. Gygax, T. K. Das Gupta and A. Eschenmoser, ibid., 55, 2205 (1972).
95) S. Shatzmiller, P. Gygax, D. Hall and A. Eschenmoser, ibid., 56, 2961 (1973).
96) S. Shatzmiller and A. Eschenmoser, ibid., 56, 2975 (1973).

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