

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

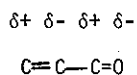
This review surveys some of the applications of various heterocyclic compounds as aids to the synthesis of molecules containing carbonyl functionality. These heterocycles are 'masked' carbonyls which can serve a dual purpose; protection of the carbonyl and/or modification of its chemical character. The 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:

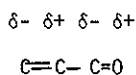
- 1) a carbonyl group results upon cleavage of the heterocycle (demasking);
- 2) this carbonyl is an aldehyde or ketone;
- 3) the heterocycle is such that there is the potential for generation of either a positive or negative charge at the carbonyl carbon atom;
- 4) alkylation of the heterocycle must 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, thio-acetal 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

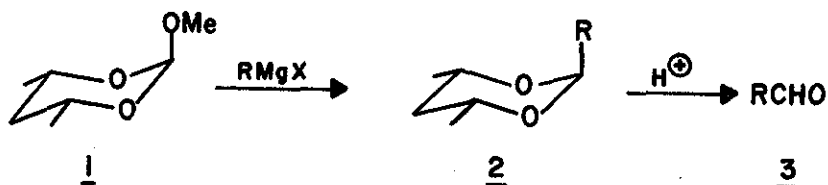
Within each of the two main divisions noted above, the further distinction as to whether alkylation occurs at the masked carbonyl, α to this position, or β to it was made.

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.

(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 Polarization1) 1,3-Dioxanes

Treatment of 2-methoxy-1,3-dioxanes 1, in which the methoxy substituent has the axial configuration, with a Grignard reagent afforded¹ 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



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

<u>RMgX</u>	<u>% 2</u>
Me-	70%
Et-	75
i-Pr-	63
ϕ -	95
p-F- ϕ -	94
p-Br- ϕ -	55
p-CF ₃ - ϕ -	89

2) Quinazolines

Grignard formylation is also feasible via the quinazoline methiodide 4², 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).

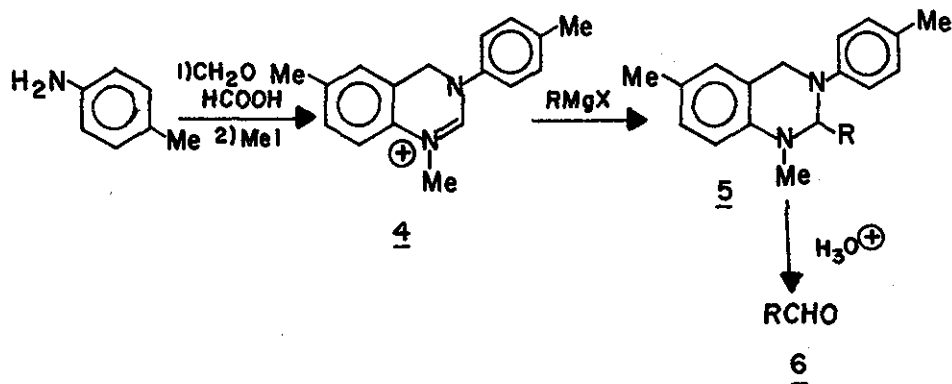


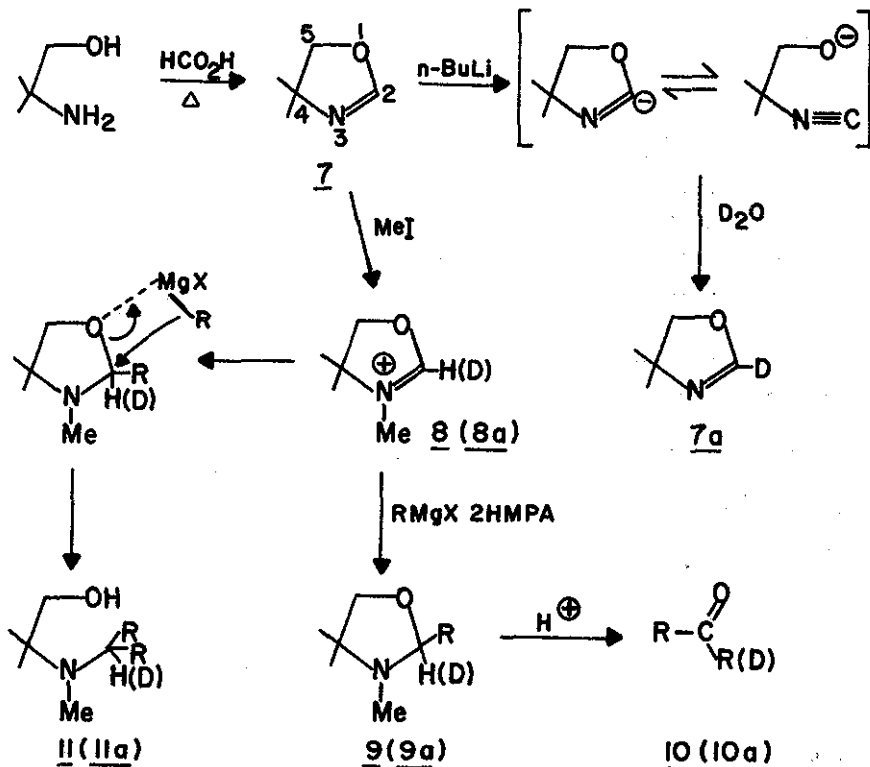
Table 2

Aldehydes prepared via the quinazoline methiodide 4

RMgX	Product (isolated as DNP derivative)	Yield
CH ₃ MgI	CH ₃ CHO	78%
n-C ₄ H ₉ MgBr	n-C ₄ H ₉ CHO	87
φCH ₂ MgCl	φCH ₂ CHO	74
n-C ₁₂ H ₂₅ MgBr	n-C ₁₂ H ₂₅ CHO	73
Et(Me)CHMgBr	Et(Me)CHCHO	34
Me ₂ CHMgBr	Me ₂ CHCHO	45
φMgBr	φCHO	95
p-CH ₃ O-φMgBr	p-CH ₃ O-φCHO	80
2,5-(CH ₃ O) ₂ -φMgBr	2,5-(CH ₃ O) ₂ -φCHO	34

3) 2-Oxazolines³

A third heterocycle which allows Grignard formylation is the substituted 2-oxazoline, 7⁴, which can be prepared⁵ 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 D₂O 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.

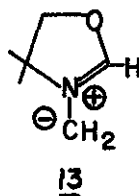
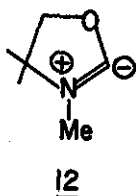
Thus this method provides a simple synthesis of aldehydes and C-1 deuterated aldehydes. However, it is limited to Grignard reagents with an sp^2 or sp hybridized carbanion. The base strength of aliphatic Grignards in HMPA is

Table 3

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

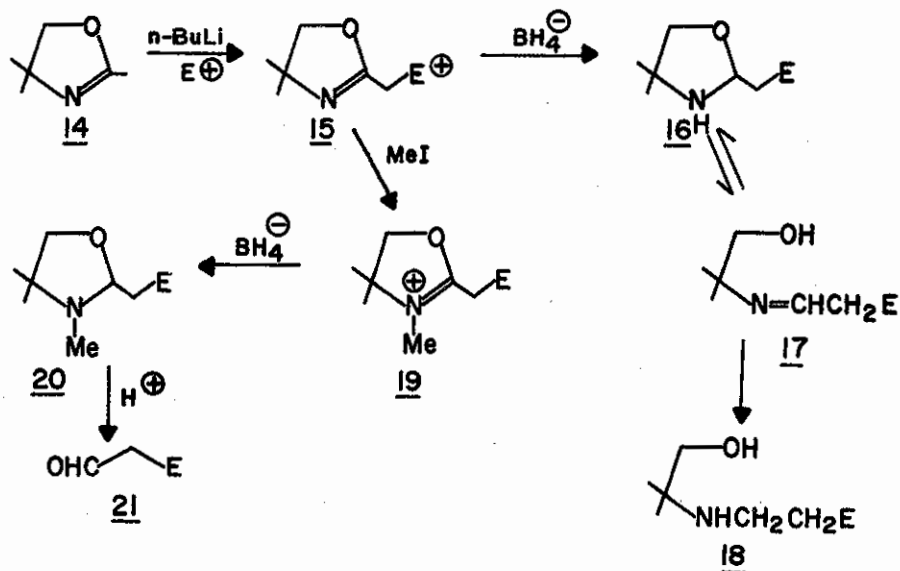
<u>RMgX</u>	<u>% 10 (10a)</u>
ϕCH_2-	87
$\phi CH=CH-$	64
$\phi C\equiv C-$	51
$o-(MeO)-\phi-$	90 (70)

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



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 well⁶⁻⁸. 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 electrophiles⁶. 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 ketones⁷. 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

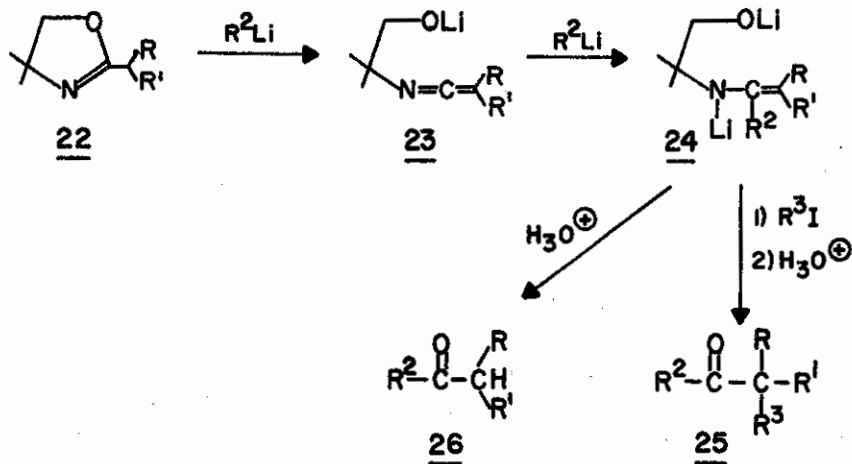


Table 4

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

<u>R</u>	<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>Yield (25 or 26)</u>
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

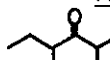
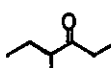
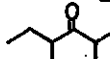
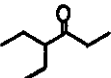
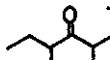
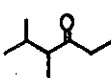
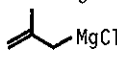
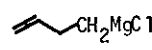

the reaction mixture is allowed to warm, rearrangement to the ketenimine 23 occurs. The second equivalent then adds to 23, affording an alkylated lithio-enamine. This addition takes place at the 'carbonyl' carbon. A second addition α to this position occurs if 24 is quenched with an alkyl halide. Acid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

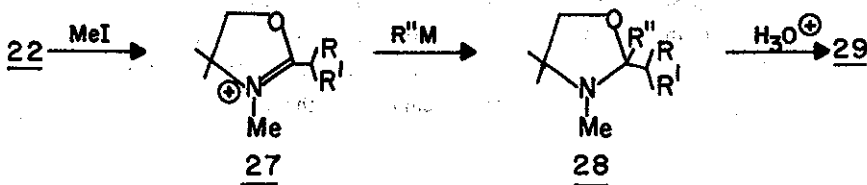
24 can itself be hydrolyzed to 26, an α,α -disubstituted ketone.

A similar ketone synthesis was accomplished by reacting the methiodide 27 of 22 with organometallic compounds⁷. 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 products⁸ (Table 5).

Table 5

Ketones synthesized from 2-oxazoline methiodides (27)

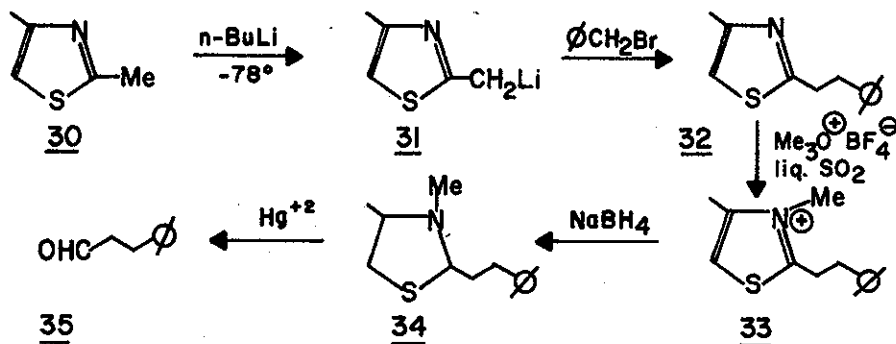
<u>R</u>	<u>R'¹M</u>	<u>R''M</u>	<u>% 29</u>	<u>Product</u>
Me	Et	i-PrLi	76%	
Me	Et	EtMgBr	64	
Me	Et	t-BuMgBr	0	—
Me	Et	i-PrMgBr	93	
Et	Et	EtMgBr	77	
Et	Et	t-BuMgBr	0	—
Et	Et	i-PrLi	88	
i-Pr	Me	EtMgBr	73	
i-Pr	Me	t-BuMgBr	0	—
Me	Et		38	sec-Bu-C(=O)-CH=C(CH ₃) ₂
			62	sec-Bu-C(=O)-CH ₂ -C(CH ₃)=CH ₂
Me	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 borohydride⁹. 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 aldehydes¹⁰. 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.



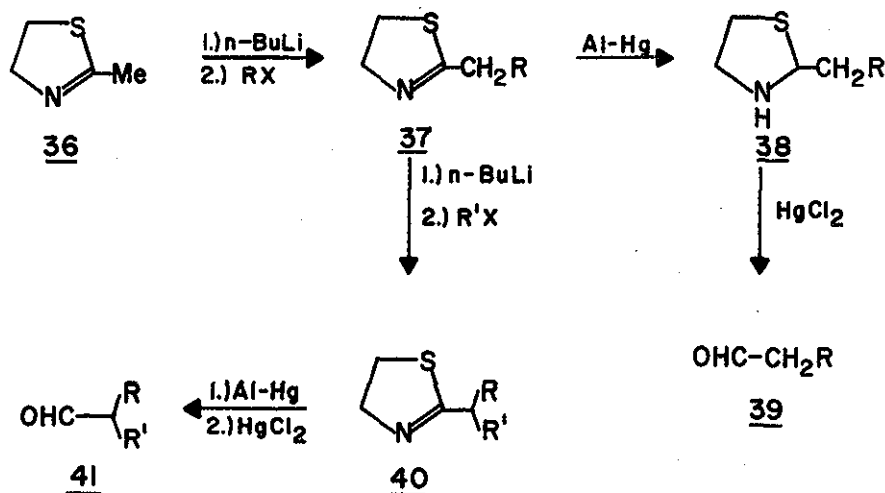
Proton abstraction from the 2-methylthiazole **30** was accomplished with n -butyllithium at -78° and the metallated species was alkylated with benzyl bromide. Quaternization at nitrogen, followed by reduction, gave the saturated heterocycle **34**, a thiazolidine. The aldehyde was liberated under neutral 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 ($<-50^\circ$), but dimerization occurred if the reaction mixture was allowed to warm¹¹⁻¹³.

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.

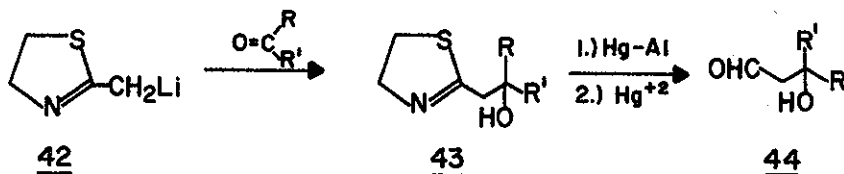
The monosubstituted products 39 were prepared in 50 to 60% overall yield.

Table 6

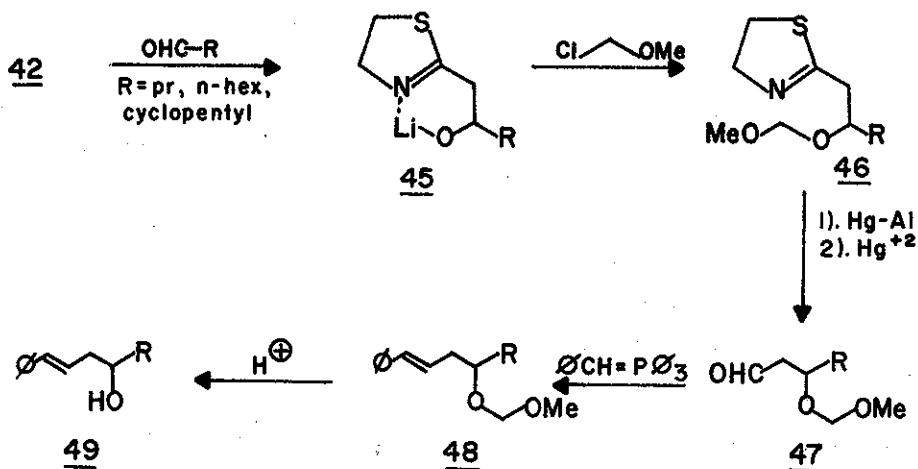
α -Substituted acetaldehydes from the thiazoline 36

<u>R</u>	<u>R'</u>	<u>R''</u>	<u>Aldehyde</u>
ϕCH_2-	--	--	
$\phi(\text{CH}_2)_3-$	--	--	
$\text{CH}_2=\text{CBrCH}_2-$	--	--	
$\phi\text{CH}=\text{CHCH}_2-$	--	--	
n-Bu	--	--	
Me	ϕCH_2-	--	
ϕCH_2-	Et	--	
Me	Me	ϕCH_2-	
Me	Me	n-Bu	
————— $(\text{CH}_2)_2$ ———		--	
————— $(\text{CH}_2)_5$ ———		--	
————— $(\text{CH}_2)_5$ ———		Me	

Because of the neutral conditions employed to unmask the aldehyde, Meyers' group extended the thiazoline route to the synthesis of β -hydroxyaldehydes^{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.



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



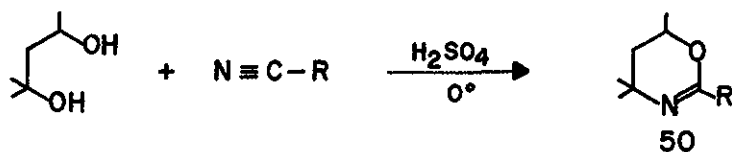
The alcohol function was most suitably protected by reacting the lithio adduct 45 with chloromethyl methyl ether.

6) Dihydro-1,3-oxazines

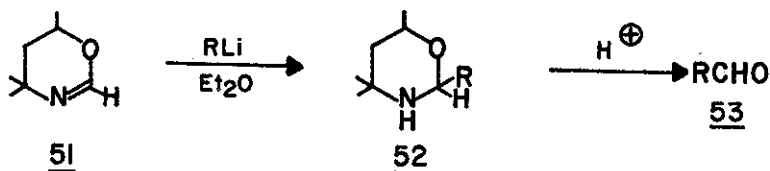
Dihydro-1,3-oxazines have proved extremely versatile in syntheses of aldehydes and ketones, for, according to the conditions employed, alkylation can be effected at the 'carbonyl' carbon, α to this site, or β to it³.

2-Substituted 4,4,6-trimethyldihydro-1,3-oxazines 50 are readily available¹⁶⁻¹⁸, with most of the preparations involving condensation of

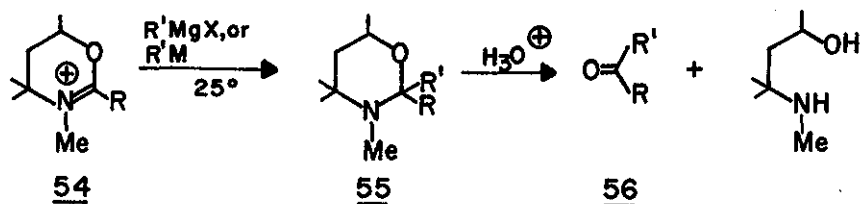
carboxylic acids, nitriles, or amides with amino alcohols, olefins, or glycols. In their extensive work on oxazine chemistry, Meyers' group found¹⁹ the condensation of a glycol with a nitrile in sulphuric acid¹⁶ to be the method of choice.



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 52²⁰. 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.



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 organolithium 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



(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=CH₂CH₂φ).

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

<u>R</u>	<u>R'M</u>	<u>% 56</u>
φCH ₂ CH ₂ -	EtMgBr	78%
φCH ₂ CH ₂ -	n-BuMgBr	71
φCH ₂ CH ₂ -	n-BuLi	51
φCH ₂ CH ₂ -	t-BuLi	29
φ-	EtMgBr	70
CH ₂ =CHCH ₂ C(φ)H	MeMgBr	56
cyclopropyl	n-BuMgBr	35

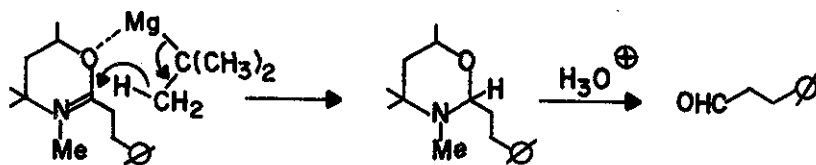


Fig. 1

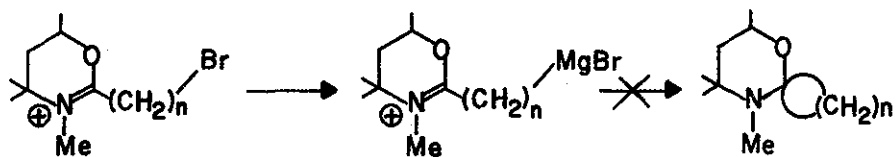
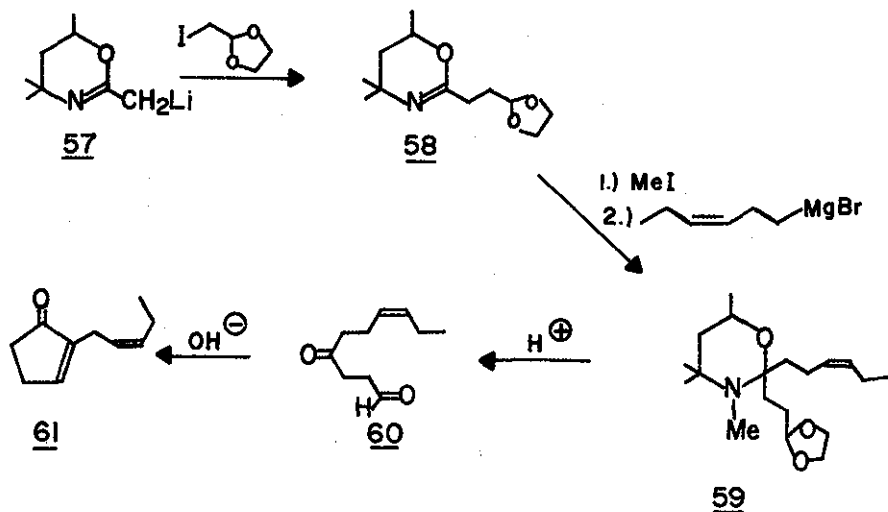


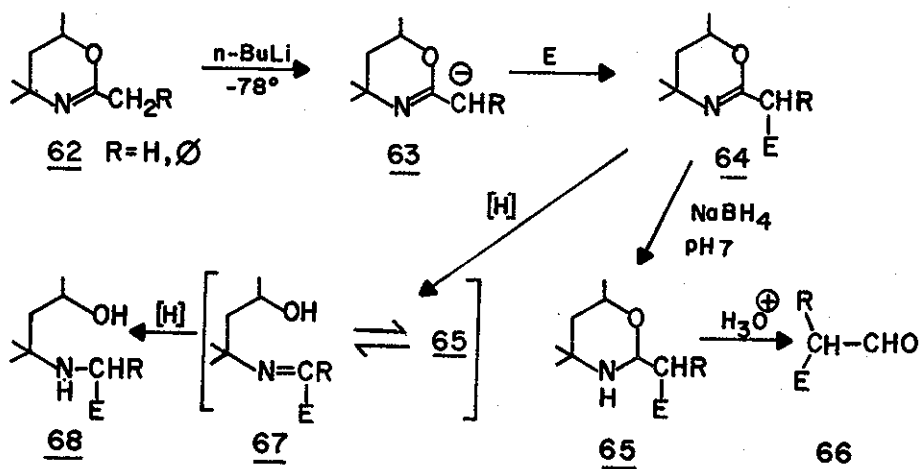
Fig. 2

A versatile synthesis of substituted cyclopentenones has been devised²³ 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

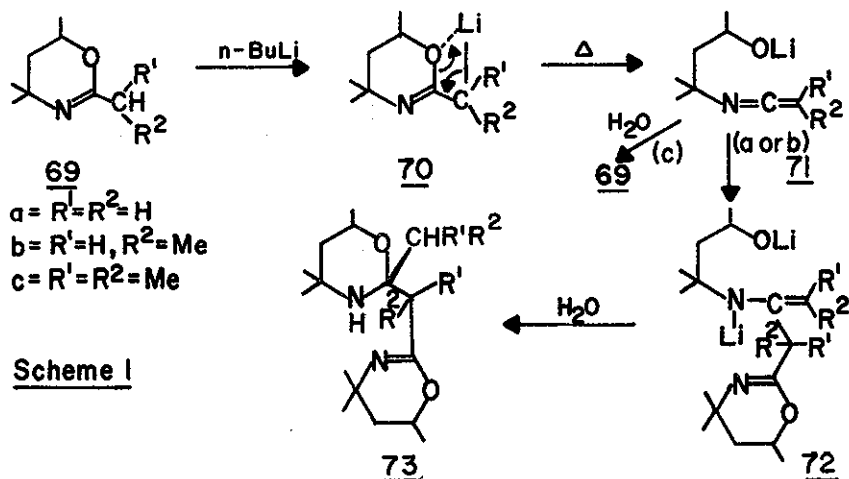
α,α -Disubstituted acetaldehydes from dihydro-1,3-oxazines

Oxazine	R'X(E)	% <u>66</u>
<u>62</u> , R=H	MeI	60%
	n-PrI	65
	n-BuI	67
	allyl bromide	53
	2-bromoethyl ether	54
	i-PrI	47
	$\emptyset\text{CH}_2\text{Br}$	54
	3-bromocyclohexene	50
<u>62</u> , R= \emptyset	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= \emptyset , CO_2Et). With secondary and tertiary carbons, the anion is only formed at a temperature

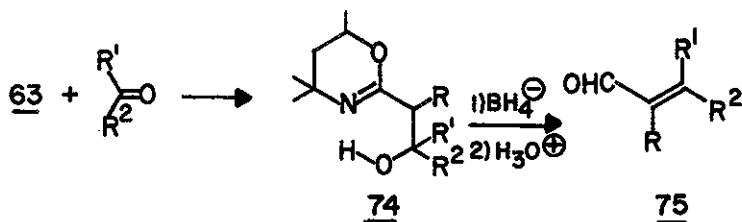
at which it is unstable. Rearrangement ensues and alkylation cannot compete meaningfully (71 does not react with electrophiles). When the carbanion is primary or secondary, dimerization occurs at the elevated temperatures, as is represented in Scheme 1.

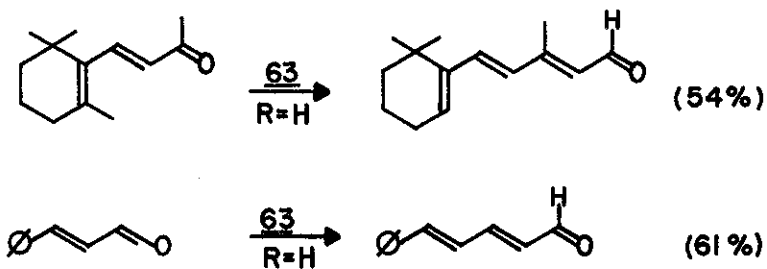
In the above synthesis (62-66), primary alkyl bromides and iodides gave good yields, although chlorides could be used if they were activated (e.g. $\phi\text{CH}_2\text{Cl}$, $\text{CH}_2=\text{CHCH}_2\text{Cl}$, $\text{CH}_3\text{CH}_2\text{C}\equiv\text{CCH}_2\text{Cl}$). However, secondary halides produced



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 obtained²⁷ from the reaction of epoxides with 63.

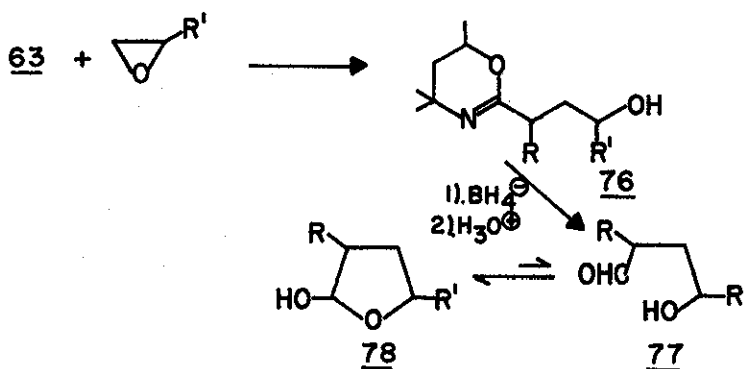


Table 9

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

Oxazine	Epoxide	% (77 & 78)
<u>63</u> , R=H	ethylene	63%
	styrene	68
	cyclohexene	57
<u>63</u> , R=φ	ethylene	69
	styrene	61
	cyclohexene	59

For dihydro-oxazines in which the anion generated was further stabilized (e.g. 63, R=φ, CO₂Et), successive alkylations at this position could be carried out with dihalides, leading ultimately to alicyclic aldehydes²⁸. The sequence is illustrated:

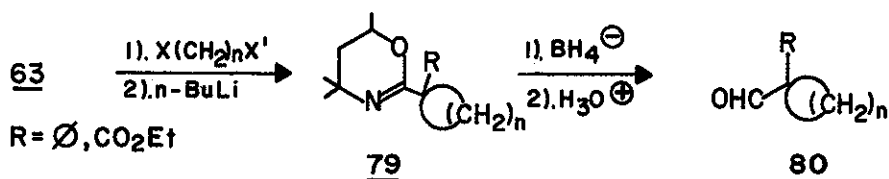
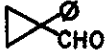
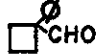


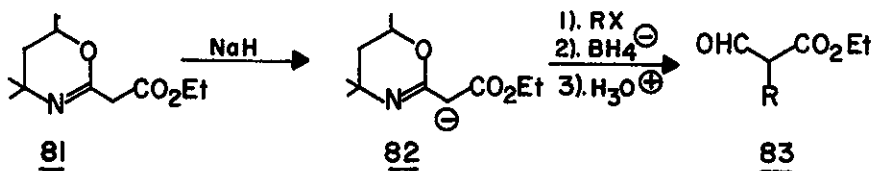


Table 10

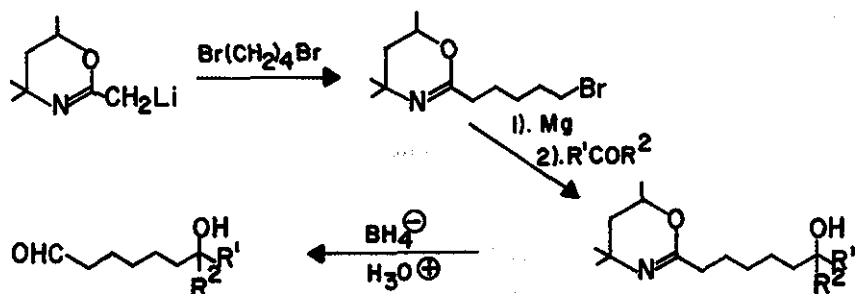
Alicyclic aldehydes from dihydro-1,3-oxazines

Oxazine	Dihalide	Aldehyde	% <u>80</u>
<u>63</u> , R=φ	1,2-dibromoethane		62%
<u>63</u> , R=φ	1,3-dibromopropane		49
<u>63</u> , R=φ	1,4-dibromobutane		60
<u>63</u> , R=CO ₂ Et	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 hydrolysis¹⁹. In this instance, sodium hydride was used to generate the doubly stabilized carbanion 82.

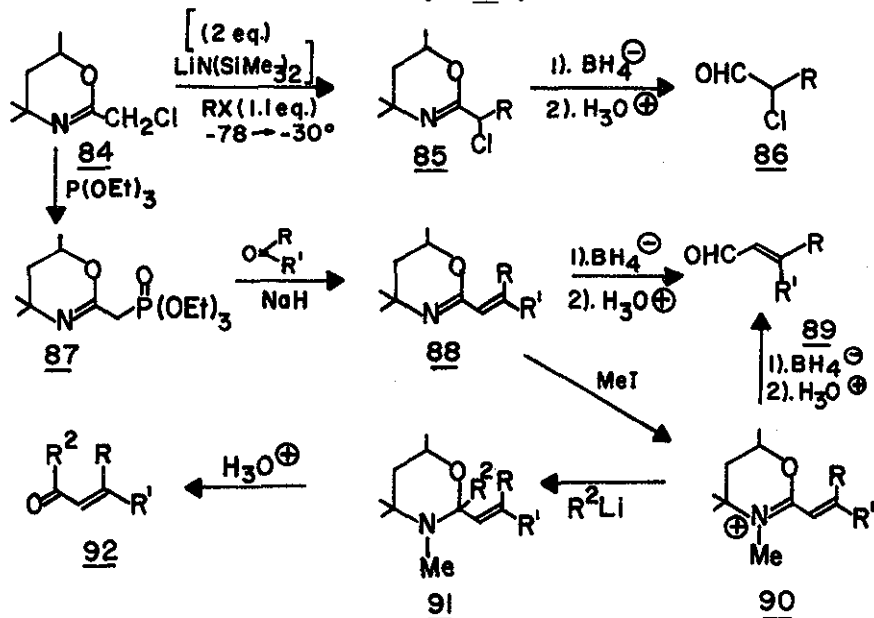


The oxazine carbonyl synthesis also allows elaboration of the side chain¹⁹. Since the heterocycle is inert to Grignards, these reagents can be used to modify other sites in the synthon. An example of this application is shown in Scheme 2.



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 methods²⁹.



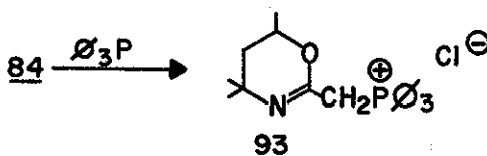
Alternatively, 84 could be converted into the phosphonate ester 87³⁰ which reacted with carbonyl compounds³¹ giving unsaturated oxazines⁽⁵⁾. These in turn afforded the α,β -unsaturated aldehydes. Conjugated ketones were also prepared via the N-methyl quaternary salt 90. Alkyl lithium reagents added in the normal manner and acid hydrolysis gave 92. Overall yields ranged from 50 to 80%.

Table 11

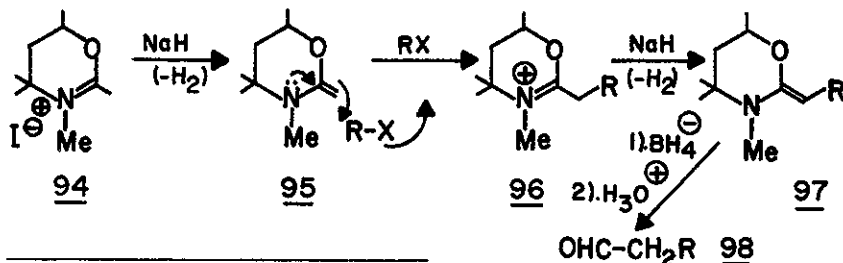
Product composition from the alkylation of 84
in lithium bis(trimethylsilyl) amide

RX	DHO-CH ₂ Cl (<u>84</u>)	DHO-CHRC1 (<u>85</u>)	DHO \rightleftharpoons 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-butyllithium³². 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
∅	H	H	80%	94%
∅	Me	H	57 (24:76,c:t)	70 (50:50,c:t)
∅	∅	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-C ₅ H ₄ N	H	H	65	72
H	∅	Me		
Me	Me	Et		
————(CH ₂) ₄ ————		Et		

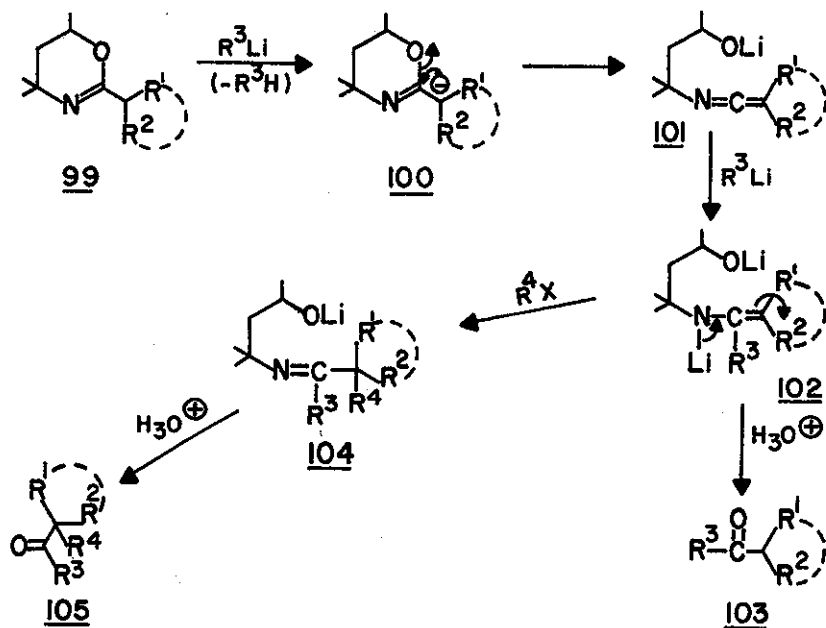
Table 13

 Substituted acetaldehydes via alkylation of 94
 (using sodium hydride)

RX	Aldehyde (98)	Yield
∅(CH ₂) ₃ I	OHC(CH ₂) ₄ ∅	51%
H ₂ C=C(Br)CH ₂ Br	OHC(CH ₂) ₂ C(Br)=CH ₂	60
∅CH ₂ Br	OHCCH ₂ CH ₂ ∅	58

The instability of the oxazine carbanion 100 at elevated temperatures ($\sim 0-10^0$), 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 Stork³⁵.



Oxazines can also be alkylated β to the masked carbonyl group if the 2-vinylloxazine 106 is employed. While 106 polymerizes when treated with organometallic reagents¹⁹, 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

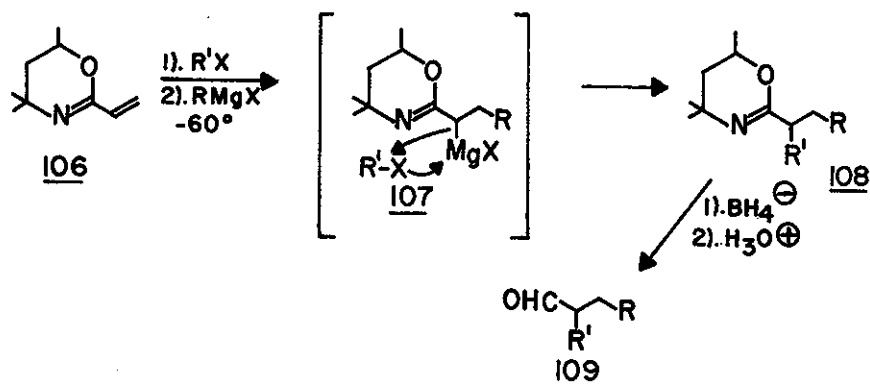


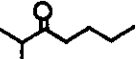
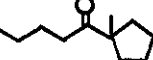
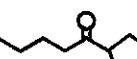
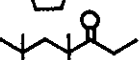
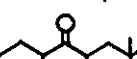
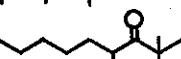
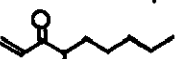
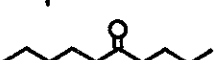
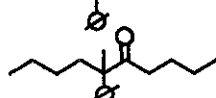


Table 14

 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	$\emptyset Li$	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
\emptyset	n-butyl	n-BuLi	-		77
\emptyset	n-butyl	n-BuLi	Me		63

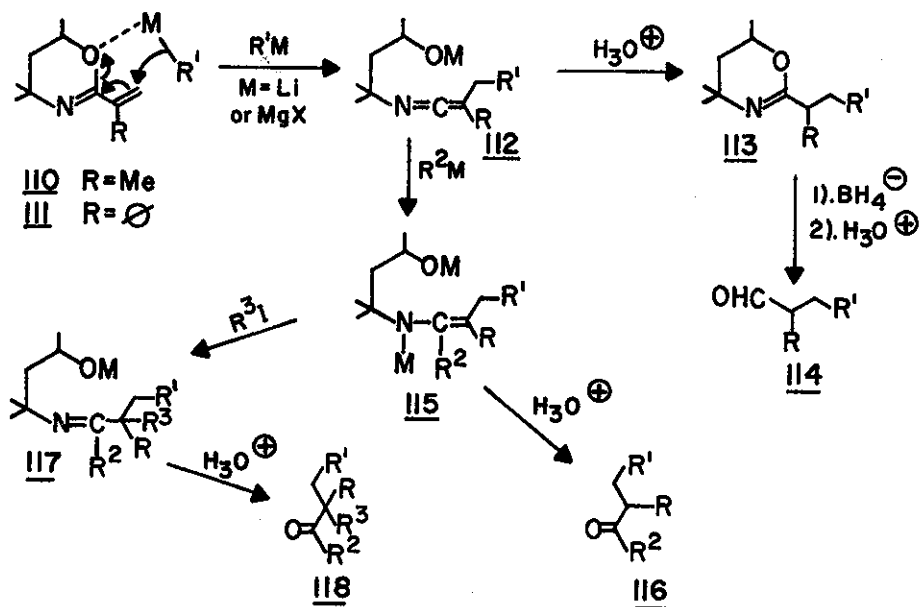
compound which has been alkylated α and β to the carbonyl group.

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 112³⁸⁻⁴⁰. 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

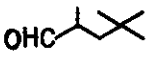
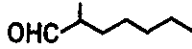
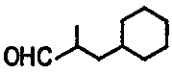
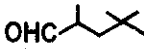
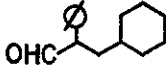
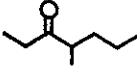
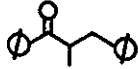
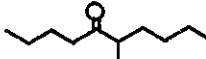
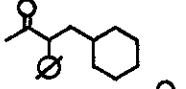
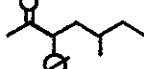
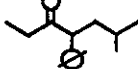
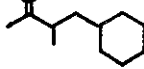
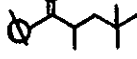
RMgBr	R'X	% 109
ϕMgBr	MeI	71
ϕMgBr	$\phi\text{CH}_2\text{Br}$	60
ϕMgBr	$\text{CH}_2=\text{CHCH}_2\text{Br}$	43
ϕMgBr		44
ϕMgBr	EtI	31
CH_3MgBr	$\phi\text{CH}_2\text{Br}$	26
EtMgBr	$\phi\text{CH}_2\text{Br}$	72
$\text{CH}_2=\text{CHCH}_2\text{MgBr}$	$\phi\text{CH}_2\text{Br}$	31



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

Table 16

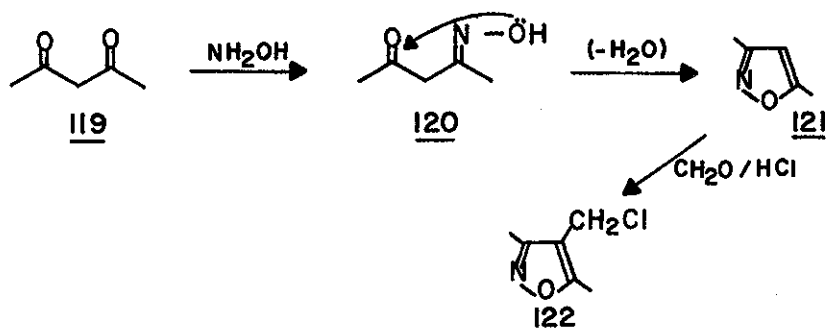
Aldehydes and ketones synthesized from the vinyloxazines 110 and 111

<u>R</u>	<u>R¹M</u>	<u>R²M</u>	<u>Product</u>	<u>Yield</u>
Me	t-BuLi			43%
Me	n-BuLi			32
Me	C ₆ H ₁₁ MgBr			78
Me	t-BuLi			71
∅	C ₆ H ₁₁ MgBr			94
Me	EtMgBr	EtMgBr		67
Me	∅MgBr	∅MgBr		47
Me	n-BuLi	n-BuLi		79
∅	C ₆ H ₁₁ MgBr	MeLi		79
∅	sec-BuLi	MeLi		65
∅	i-PrBuLi	EtMgBr		65
Me	C ₆ H ₁₁ MgBr	MeLi		82
Me	t-BuLi	∅MgBr		31

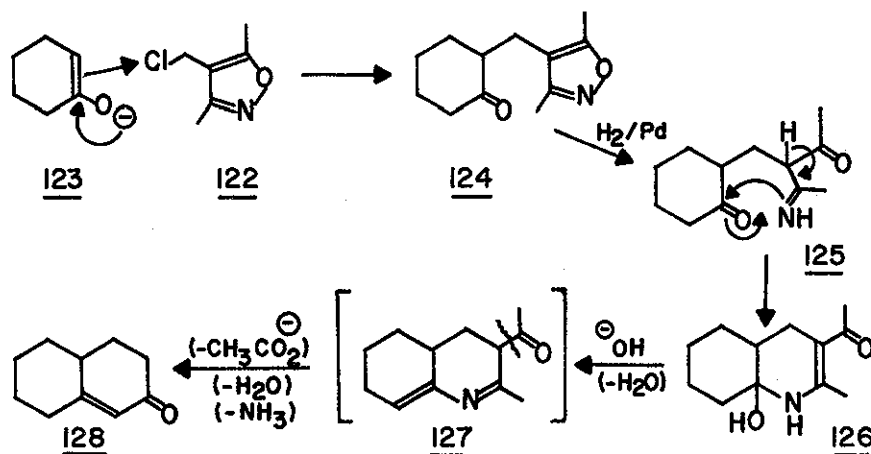
7) Isoxazoles

Isoxazole derivatives have proved useful in the synthesis of polycyclic carbonyl compounds, and, in particular, have been employed in two steroid syntheses⁴¹⁻⁴³. 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 chloromethylation⁴⁴. 122 reacts with enolates, giving 124, which is ultimately converted into the α,β -unsaturated ketone 128⁴⁵. The mechanisms for these



transformations are shown below:

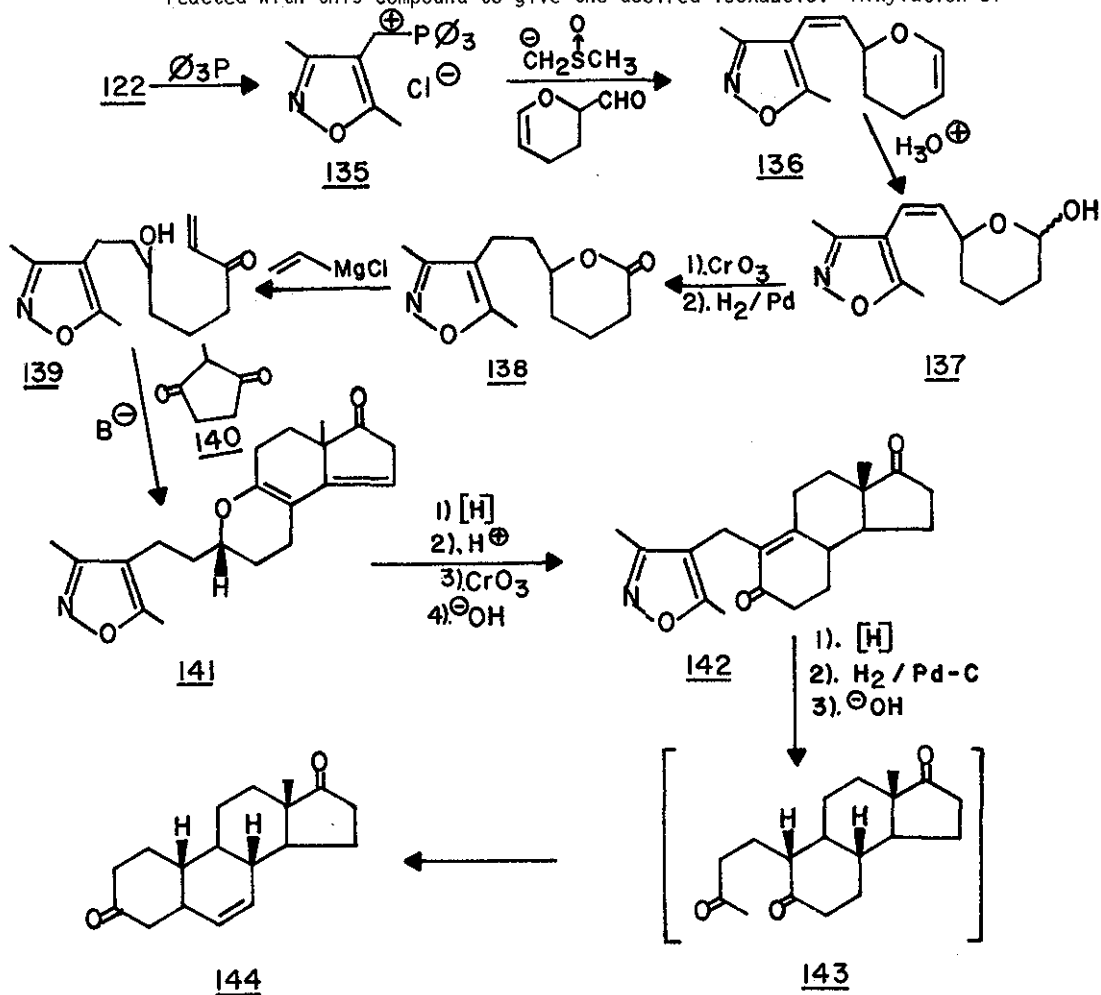


After 124 is generated, catalytic hydrogenation cleaves the N-O bond to give the imino ketone 125, which in turn cyclizes to 126. Basic hydrolysis of this compound produces a masked triketone 127. Loss of acetate from, and cyclization of, this intermediate yield 128. The sequence of steps for the conversion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

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

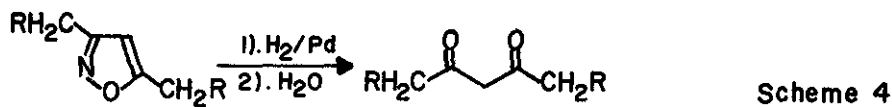
The second steroid synthesis had as its key intermediate the isoxazole 139, which was used to alkylate the 5-membered cyclic diketone 140^{42,43}. This ketone formed the D-ring of the steroid 144.

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

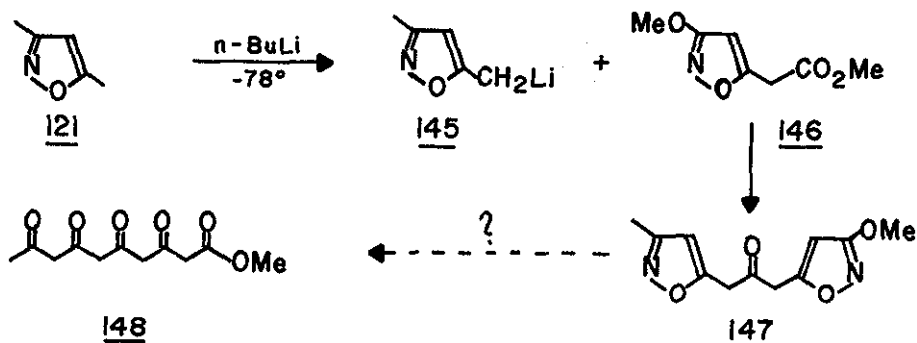


139 was successful, forming the enol ether 141. The D ring olefin was reduced, after which hydrolysis of the enol ether, Jones oxidation and cyclization gave the α,β -unsaturated ketone 142. Reduction of this olefin, catalytic cleavage of the isoxazole ring, and hydrolysis resulted in a transient triketone 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

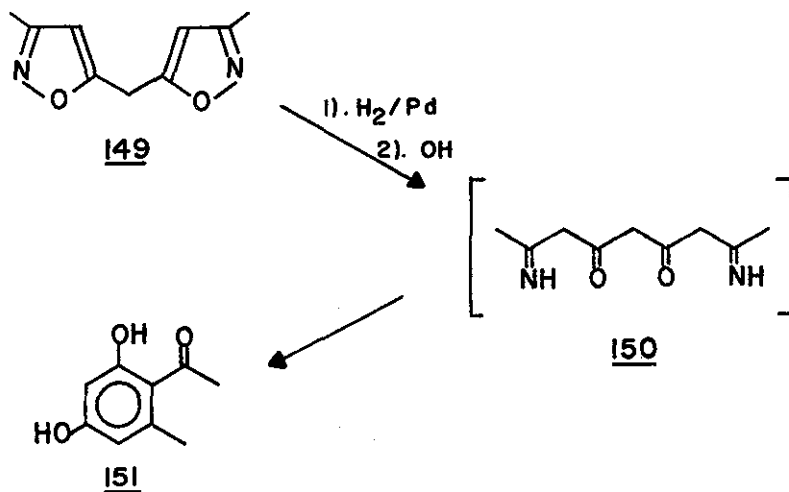


and there have been recent efforts to realize them via isoxazoles^{47,48}. Condensation of the lithio isoxazole 145 with 146 yielded the keto-bis-isoxazole 147, which can be viewed as a masked form of the tetraketo-ester



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 prepared⁴⁸, hydrogenolysis and hydrolysis of which gave the acetophenone derivative 151, presumably via the intermediate 150.

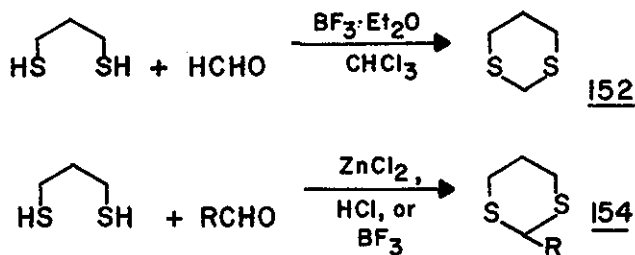


Heterocycles Yielding Reverse Carbonyl Charge Polarization

1) 1,3-Dithianes

The 1,3-dithiane system was first used as a synthetic tool in 1965⁴⁹ and has since found extensive use as a masked carbonyl capable of reacting with electrophiles⁵⁰. 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).

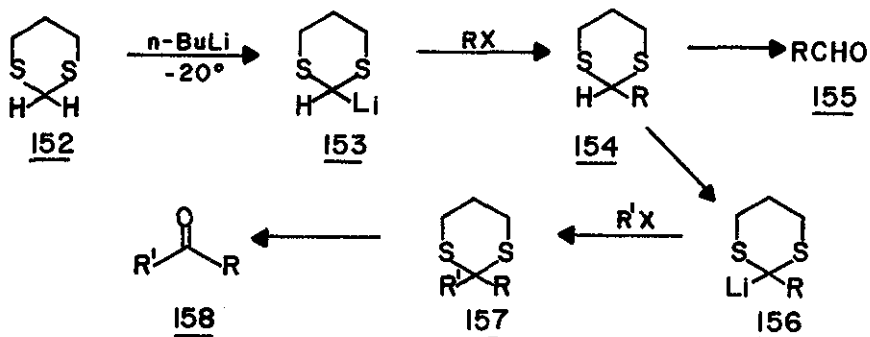
1,3-Dithiane, 152, can be prepared⁵¹ by the Lewis acid catalyzed reaction of propan-1,3-dithiol with formaldehyde. Mono-substituted dithianes 154 are similarly available⁵⁰ (Scheme 5) or can be synthesized by alkylation of 152, as is described subsequently.



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 chemistry⁵⁰ 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 Seebach⁵⁰. 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

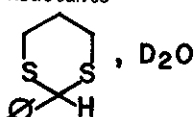
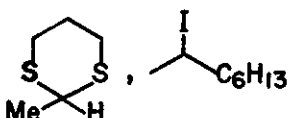
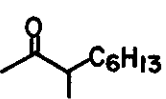
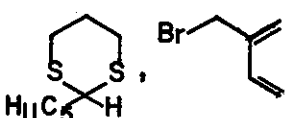
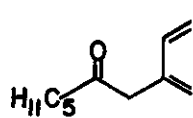
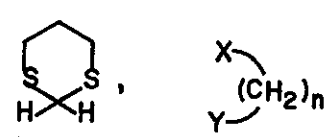
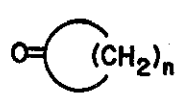
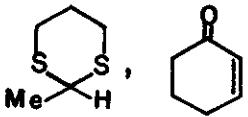
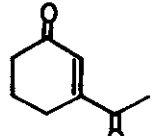
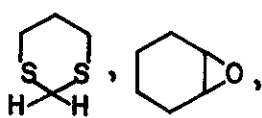
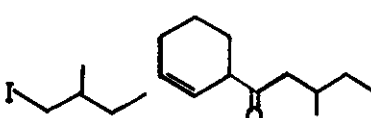
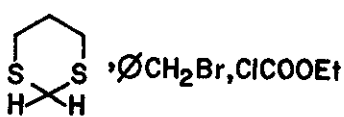
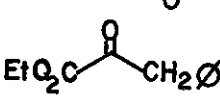
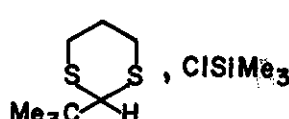
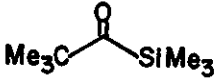
Reagents employed for the hydrolysis of 1,3-dithianes

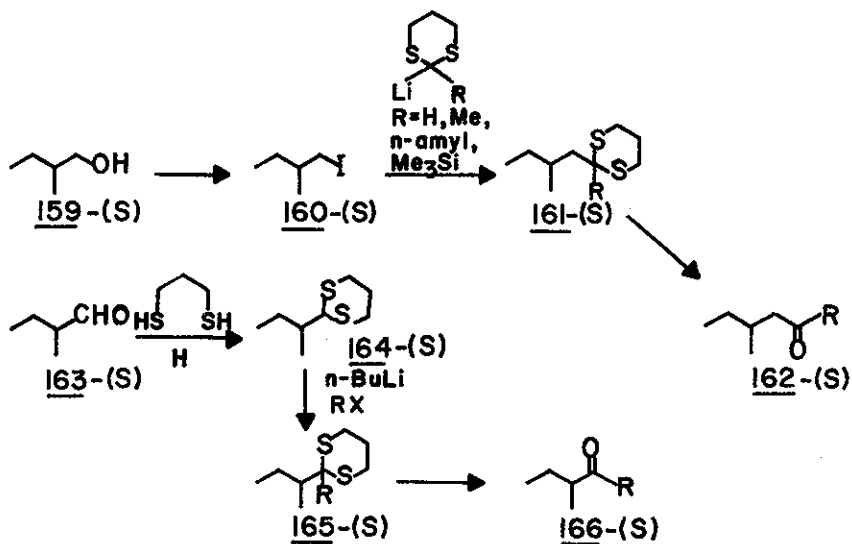
<u>Reagent</u>	<u>Conditions</u>	<u>Yield</u>	<u>Reference</u>
HgCl ₂	90% MeOH or THF 2-4h reflux	63-87%	50,52
HgCl ₂ -HgO	90-94% MeOH 1-5h reflux	60-83%	50,52
HgCl ₂ -CaCO ₃	80% MeCN or 90% MeOH	90-93%	50,52
HgCl ₂ -CdCO ₃	ØH/acetone/H ₂ O, 20h, 20 ⁰	34%	50
NBS	96% acetone, 5 min, -5 to -10 ⁰	76-97%	50,52
NBS-AgNO ₃	aqueous CH ₃ CN or acetone		52
NCS-AgNO ₃	aqueous CH ₃ CN or acetone	72-94%	50,52
HgO-BF ₃	H ₂ O-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 ₃ CN, RT, 3 min	70-85%	56
Tl(III)trifluoroacetate	RT, 5 min	77-80%	57
MeFSO ₃ / ⁰ OH	RT, 1h	62-88%	58
H ₂ SO ₄	RT, 20 min	91-95%	59
O-mesitylenesulphonyl- hydroxylamine	1) CHCl ₃ , RT, 30-60 min 2) H ₂ O	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.

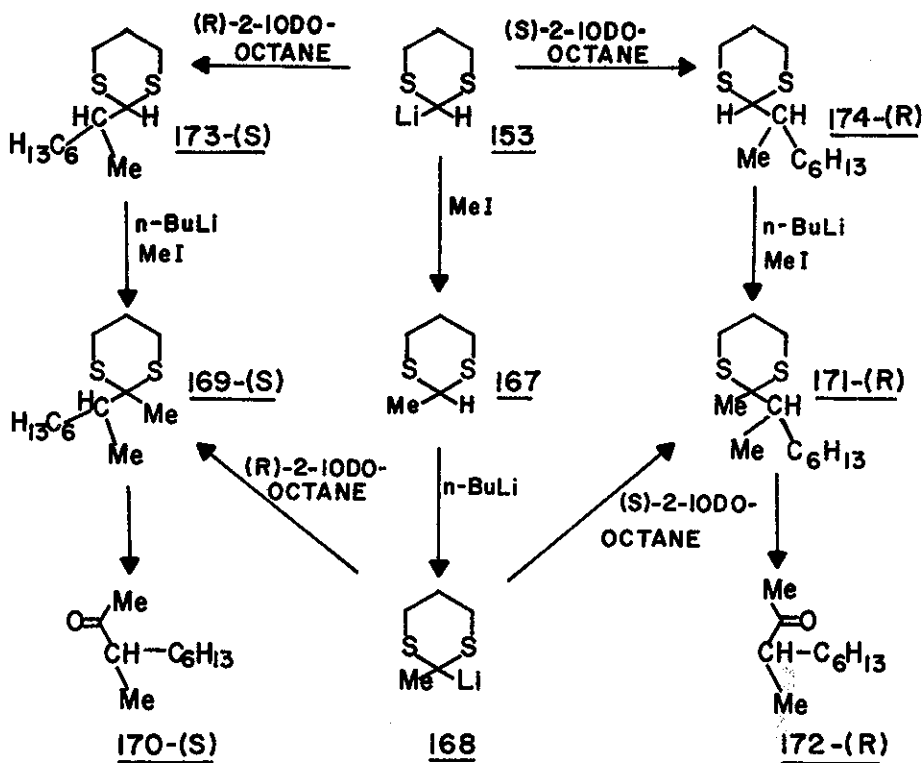
Table 18

Some representative carbonyl compounds synthesized from 1,3-dithianes

Reactants	Final Product	Reference
	$\text{C}_6\text{H}_5\text{CDO}$	61
		63
		64
		51,65
		50,52,66
		62
		50
		67

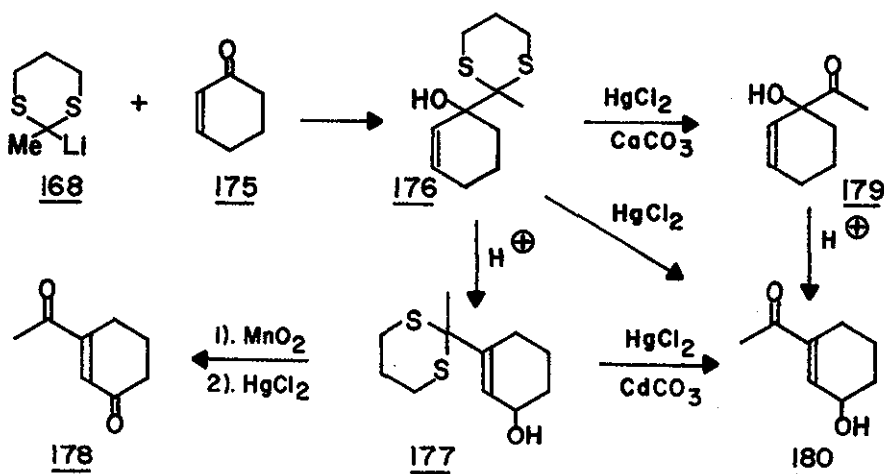


In cases where alkylation occurs by Sn^2 displacement at the asymmetric centre, inversion of configuration occurs. The optical yield is approximately



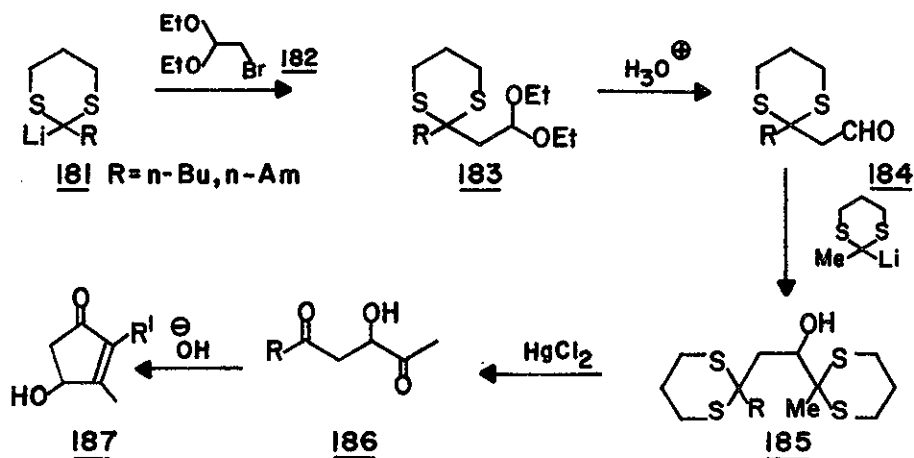
10% higher when the active halide is used to alkylate the lithio methyl-dithiane 168, rather than 153. It was reasoned⁶³ that the methyl group caused a higher degree of inversion in the alkylation.

The lithio methyl-dithiane 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.

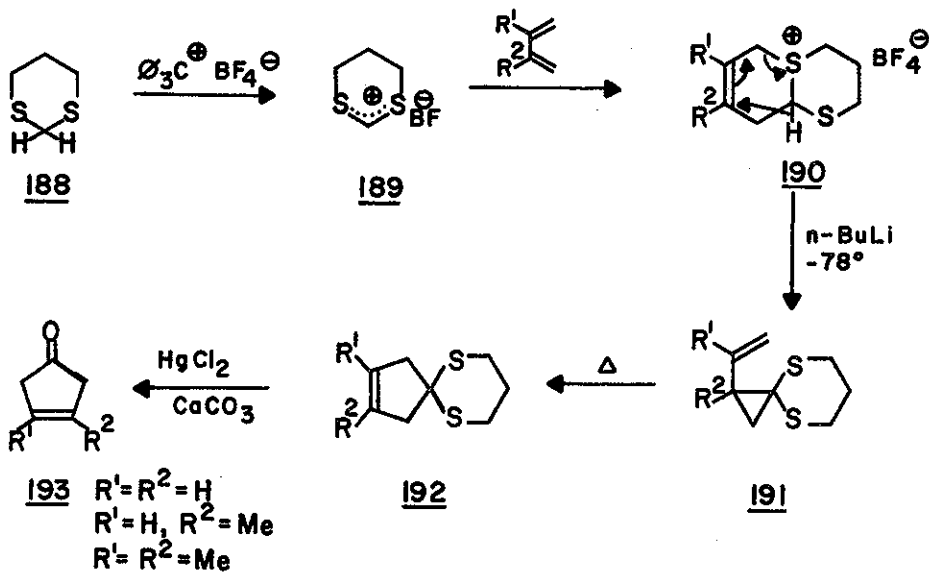


Dithianes also show promise in the synthesis of prostaglandins. Woessner and Allison have synthesized the hydroxycyclopentenone 187 using the dithiane moiety as the key tool⁶⁸. 181 was alkylated with the diethyl acetal of bromoacetaldehyde and the adduct 183 was hydrolyzed to the corresponding aldehyde. Reaction of 184 with lithio methyl-dithiane 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

Tabile α -hydroxyketone 186.



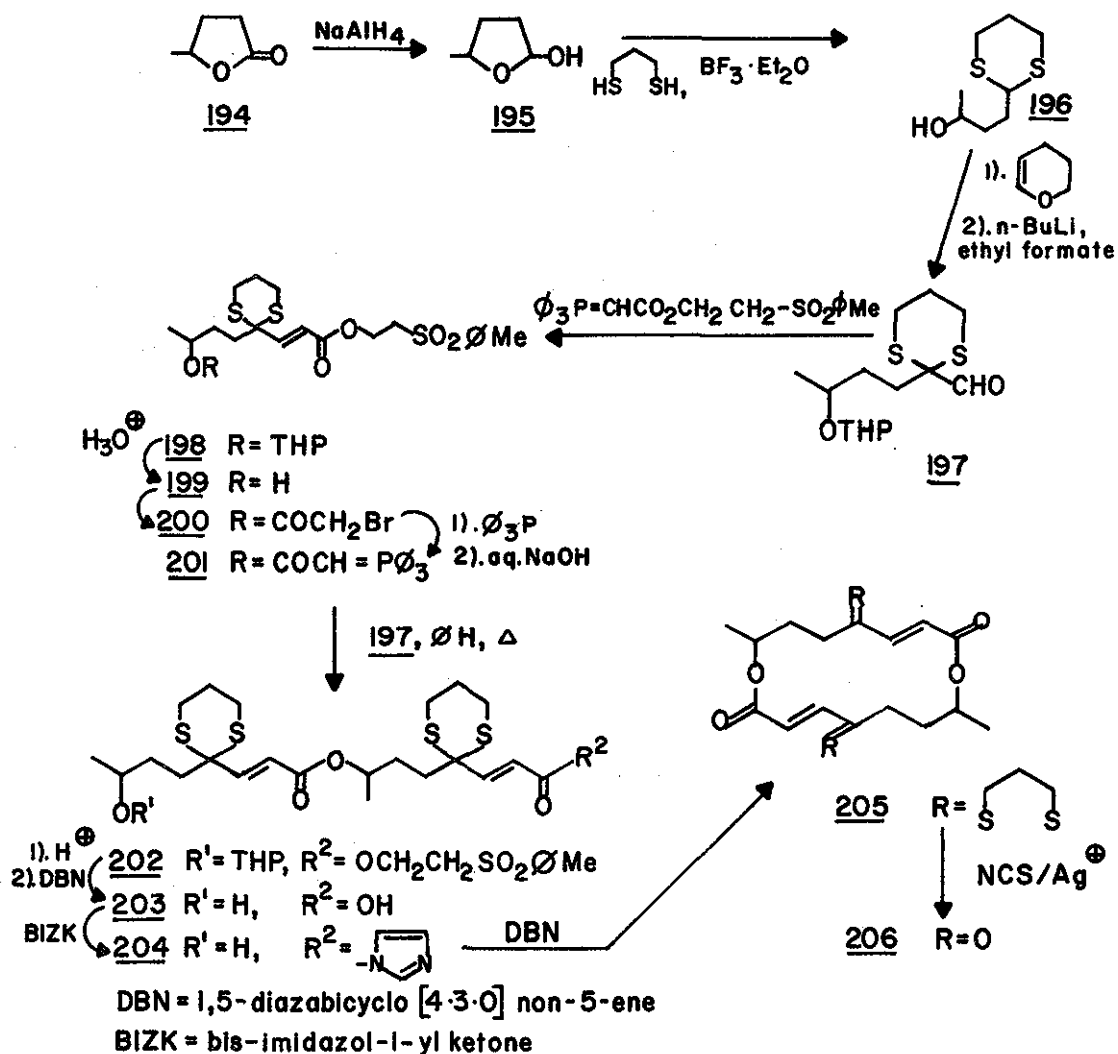
When 1,3-dithiane is treated with the fluoroborate of triphenylfluoromethane, the 1,3-dithienium salt 189 is formed⁶⁹. It in turn reacts with dienes in a cycloaddition process to give 190. A rearrangement product, a



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.

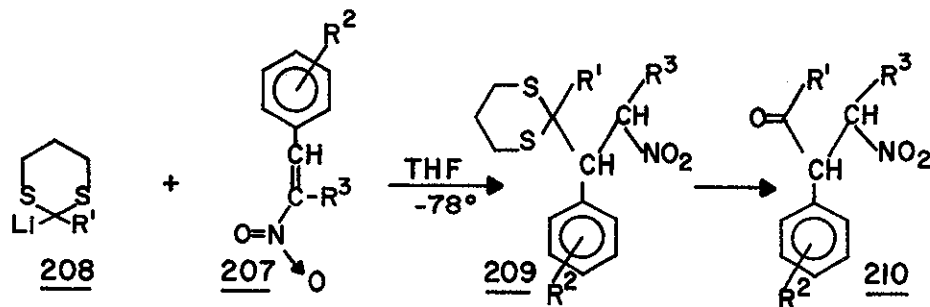
In the above sequence, 189 is in effect a masked form of carbon monoxide.

The 1,3-dithiane heterocycle has been applied to the synthesis of the macrolide antibiotic pyrenophorin, 206⁷⁰. 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 accomplished⁷¹ the 1,4-addition of 2-lithio-1,3-dithianes to substituted ω -nitrostyrenes 207 to give adducts of type 209.



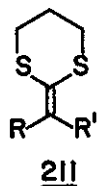
Note, however, that this is still an alkylation at the masked carbonyl. Typical results are presented in Table 19, but the authors reported that yields had not been optimized in many instances.

Table 19

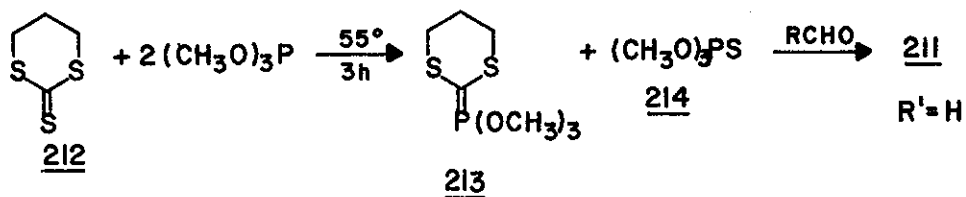
Structures and yields of nitrodithiane adducts (209)

<u>R¹</u>	<u>R²</u>	<u>R³</u>	<u>% 209</u>
H	4-CH ₃ O	H	25%
H	2,5-(CH ₃ O) ₂ -4-Me	H	90
H	4-CH ₃ O	Me	50
H	2,5-(CH ₃ O) ₂ -4-Me	Me	70
Me	4-CH ₃ O	H	25
ϕ	4-CH ₃ O	H	90
ϕ	2,5-(CH ₃ O) ₂	H	72

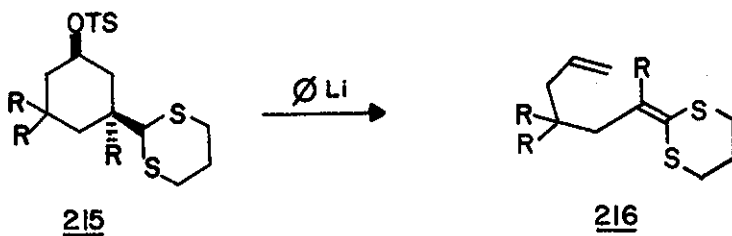
Much of the recent work in the dithiane field has involved compounds exemplified by 211, a ketene thioacetal. They had been prepared by Corey



and Markl⁷² 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.



Another non-general route to ketene thioacetals was discovered by Marshall and Belletire⁷³. Treatment of the tosylate 215 with phenyl lithium caused the elimination reaction shown, to produce 216. This was accomplished for R=H, CH₃.



A more useful procedure was arrived upon by several groups⁷⁴⁻⁷⁸ 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.

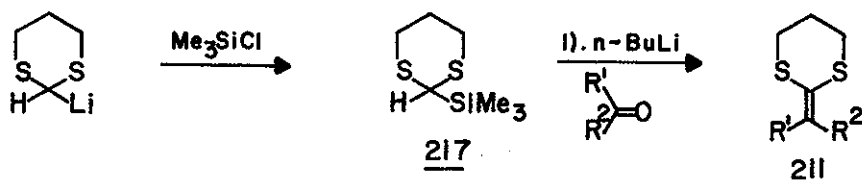



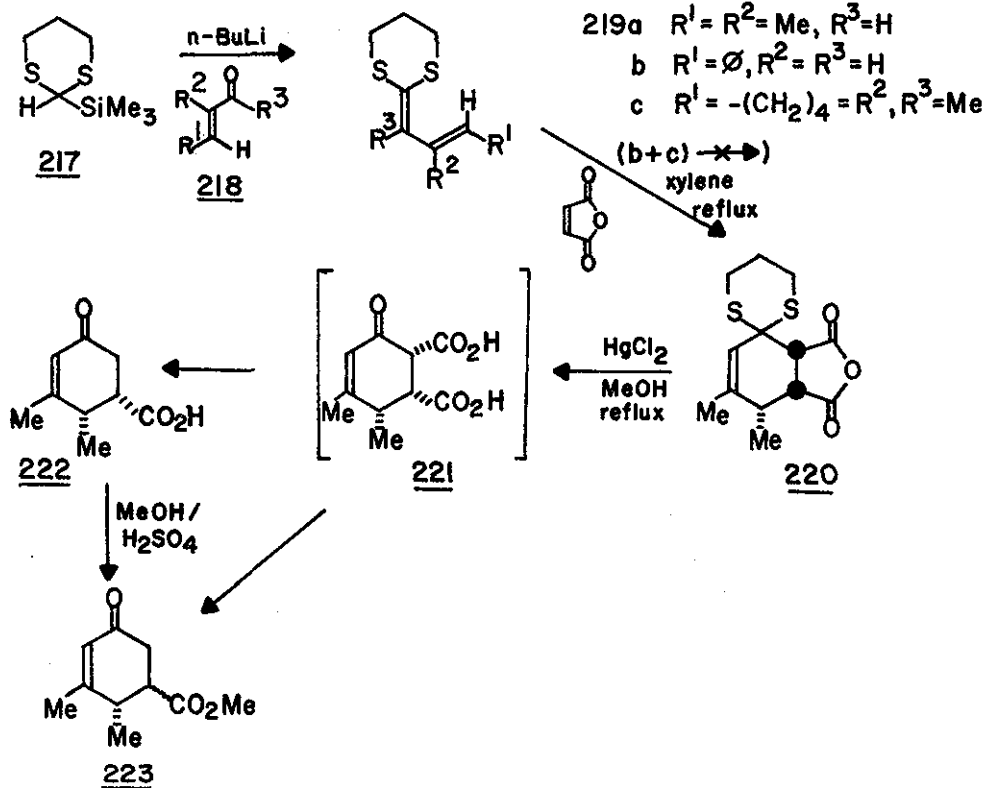
Table 20⁷⁵

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

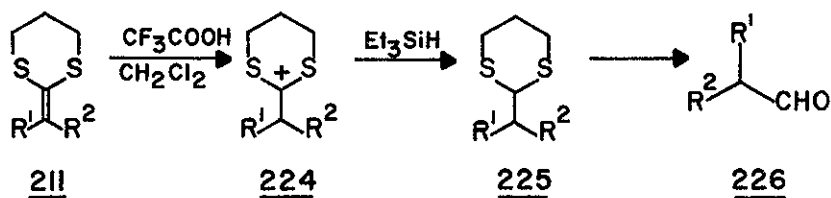
R^1COR^2	% <u>211</u>
<i>n</i> -PrCHO	67%
<i>i</i> -PrCHO	69
ϕ CH=CHCHO	66
ϕ CHO	68
MeCOMe	45
ϕ COMe	66
ϕ CO ϕ	75
	69

Using this method, Carey and Court prepared⁷⁹ 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 triethylsilane⁷⁴. Hydrolysis of 225 then gave the α,α -disubstituted aldehyde 226.



The anion 228, generated from ketene thioacetals with *n*-butyllithium in hexamethylphosphoramide, reacted with alkyl halides to give the olefinic species 229⁸⁰. Hydrolysis with *O*-mesitylenesulphonylhydroxylamine yielded the α,β -unsaturated ketone 230. Some of the ketones synthesized in this manner are presented in Table 21.

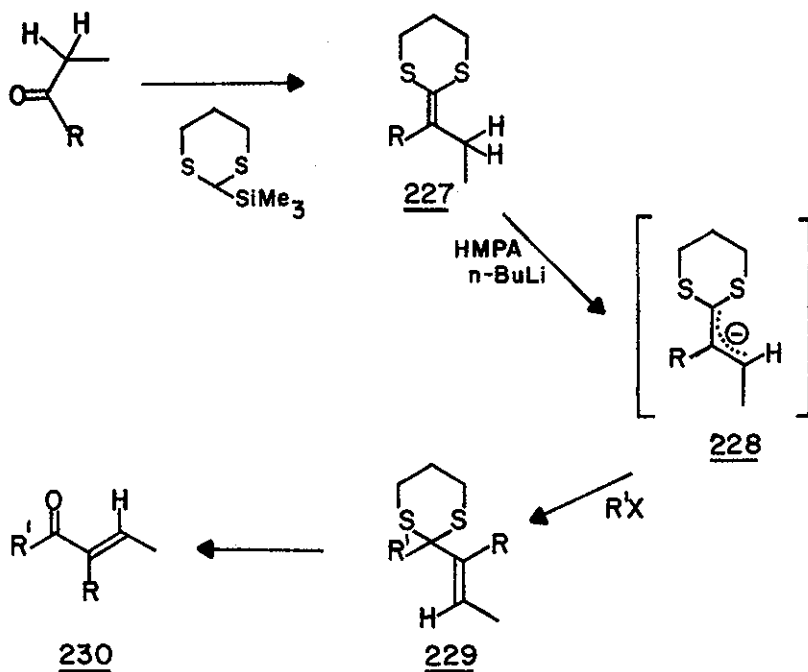
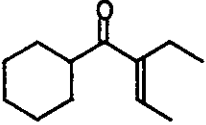
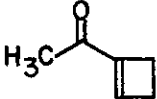
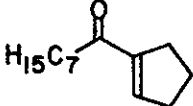
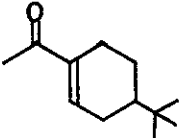
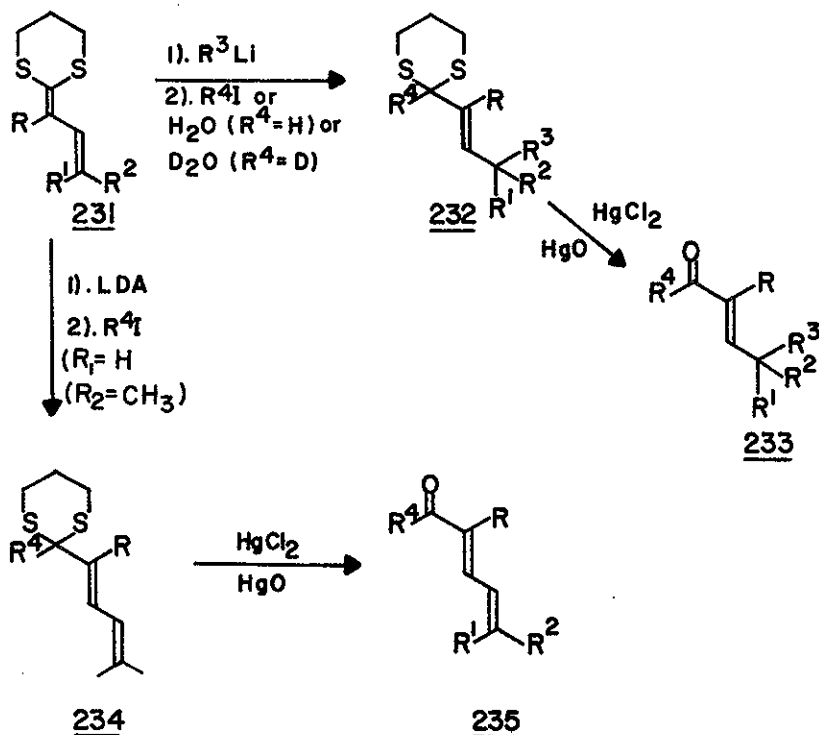


Table 21

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

<u>Ketone</u>	<u>Yield</u>
	51%
	75%
	60%
	65%

A 1,4- or 'Michael' addition to conjugated ketene thioacetals has also been realized by Seebach's group⁸¹. 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 \rightarrow 234).



Meyers' group have prepared the cyano ketene thioacetal 239⁸². Metal-lation with *n*-butyllithium and quenching of the resultant anion with an alkyl halide gave mixtures of the products 241 and 242. No further applica-tions 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 halide⁸³. 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

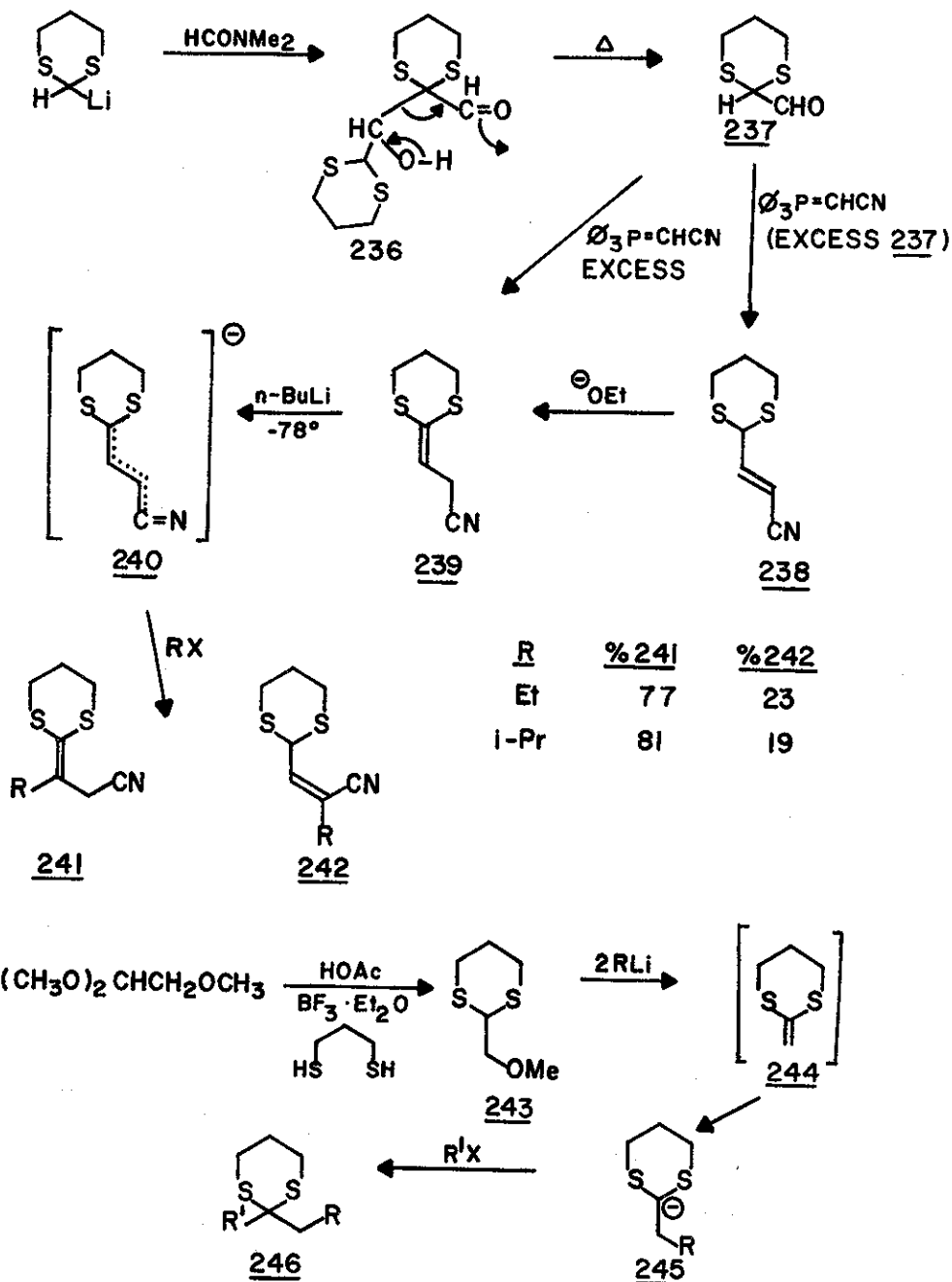
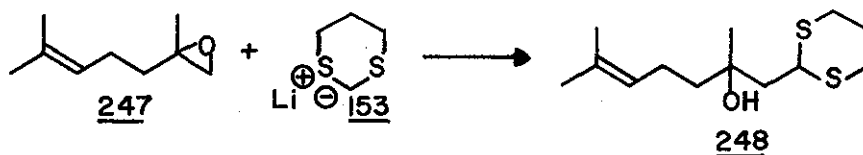


Table 22

Thioketals prepared from the methoxy-thioacetal 243

<u>R</u>	<u>R¹</u>	<u>% 246 (from 243)</u>
n-Bu	H	91%
sec-Bu	H	94
t-Bu	H	98
n-Bu	n-Am	79

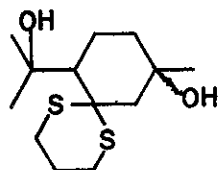
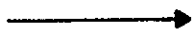
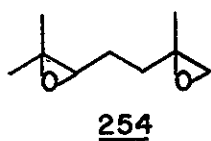
was prepared by reacting 1,2-epoxy-2,6-dimethyl-5-heptene 247 with 2-lithio-1,3-dithiane. Several transformations of 248 were effected, as seen in



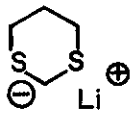
Scheme 6, and it was subsequently converted to linaloyl oxide 253.

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.

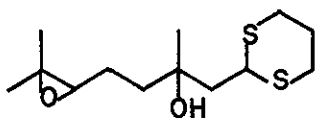
Dithianes have been employed^{83c} in a new synthesis of functionally substituted cyclopentenones. Reaction of 153 with 2,2-dialkoxynitriles 258 gave the intermediate 259 which in turn afforded the α -diketo-dithiane 260 in 50 to 70 percent yield from 258. The cyclopentenone derivatives 262 were prepared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



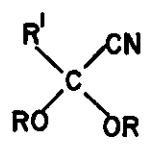
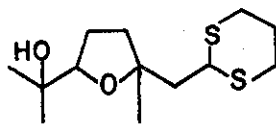
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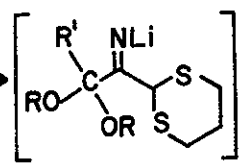
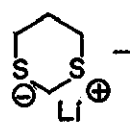
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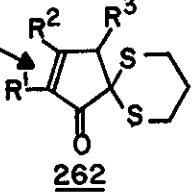
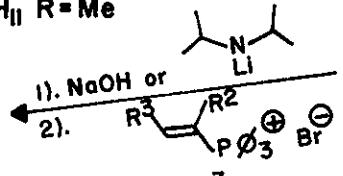
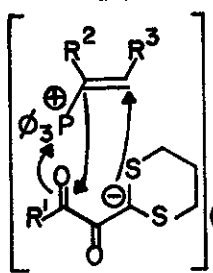
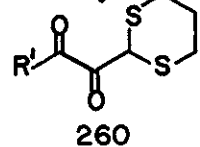
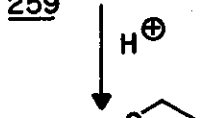
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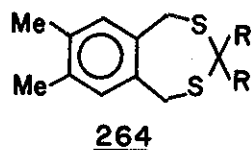
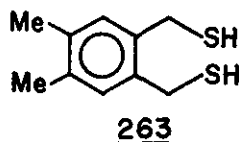


- 258 a R¹=H R=Et
- b R¹=Me R=Et
- c R¹=Et R=Et
- d R¹=n-C₅H₁₁ R=Me



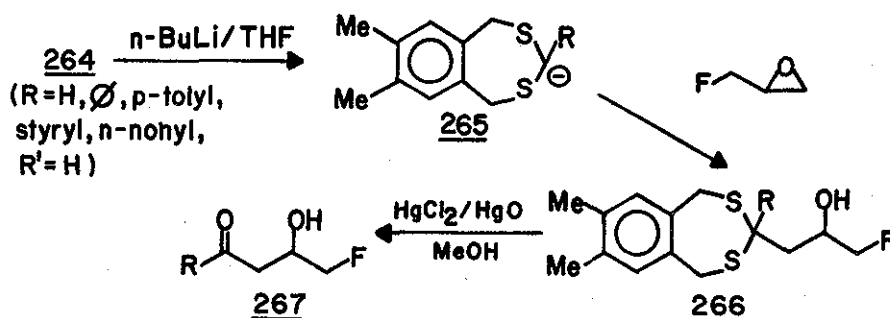
2) 1,3-Dithiepanes

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



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 chloride⁵⁴.

Table 23

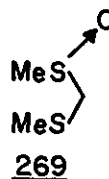
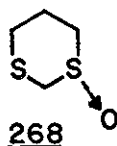
Results of 1,3-dithiepane alkylation

<u>Alkylating Agent</u>	<u>Starting Material</u>	<u>Product</u>	<u>Yield</u>
n-C ₄ H ₉ Br	<u>264</u> R=R'=H R=Me, R'=H	<u>264</u> R'=n-C ₄ H ₉ , R=H R'=n-C ₄ H ₉ , R=Me	92% 85
H ₂ C=CHCH ₂ Br	<u>264</u> R=R'=H R=Me, R'=H	<u>264</u> R'=H ₂ C=CHCH ₂ , R=H R'=H ₂ C=CHCH ₂ , R=Me	91 79
∅CH ₂ Br	<u>264</u> R=R'=H R=Me, R'=H	<u>264</u> R'=∅CH ₂ , R=H R'=∅CH ₂ , R=Me	71 50
Me Me	<u>264</u> R=R'=H R=Me, R'=H	<u>264</u> R' = $\begin{matrix} \diagup \\ \diagdown \end{matrix} \text{CH}(\text{CH}_2)_2, \text{R}=\text{H}$ R' = $\begin{matrix} \diagup \\ \diagdown \end{matrix} \text{CH}(\text{CH}_2)_2, \text{R}=\text{Me}$	75 61
n-C ₁₀ H ₂₁ Br	<u>264</u> R=R'=H R=Me, R'=H	<u>264</u> R'=n-C ₁₀ H ₂₁ , R=H R'=n-C ₁₀ H ₂₁ , R=Me	74 88

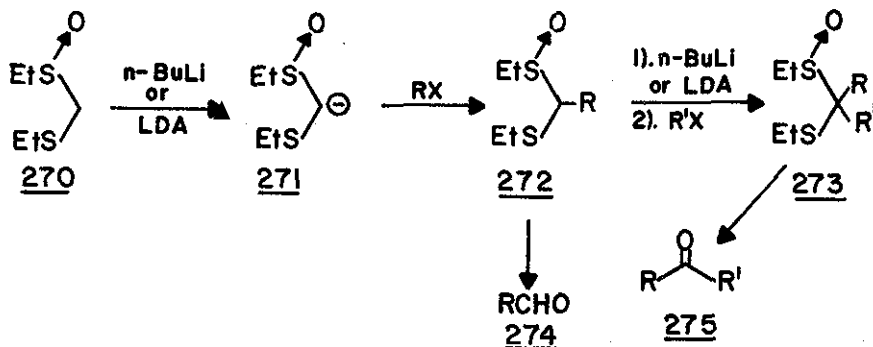
3) Thioacetal Monosulphoxides

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 268⁸⁴ and 269⁸⁵, which were said to react with electrophiles, but he could not reproduce the reported results satisfactorily⁸⁶. However, the diethyl analogue of 269 gave the anion 271



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

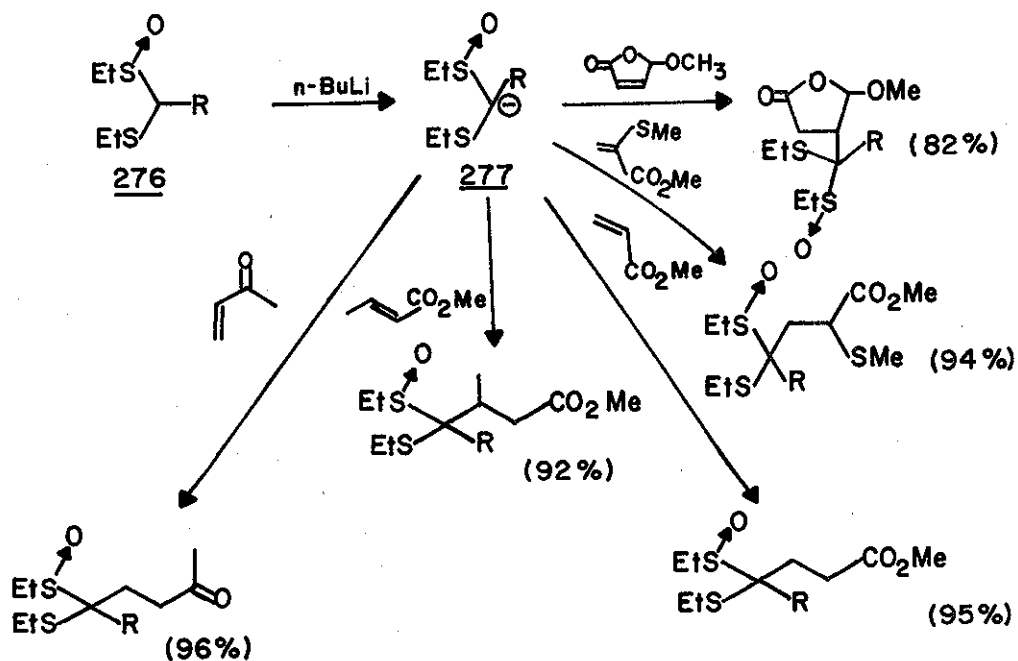


or 273 gave the corresponding aldehyde or ketone. The deblocking was performed in quantitative yield with a catalytic amount of 70% perchloric acid, but there was a problem of contamination with ethyl disulphide. This presented difficulties with aldehydes or ketones having a boiling point of less than 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.

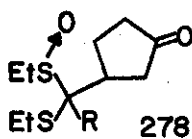
The thioacetal monosulphoxide 270 was prepared by reacting formaldehyde with ethyl mercaptan and oxidizing the thioacetal produced with metaperiodate.

Schlessinger also found that the anion 271 would add in a 1,4-fashion to α,β -unsaturated carbonyl compounds⁸⁷. 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.

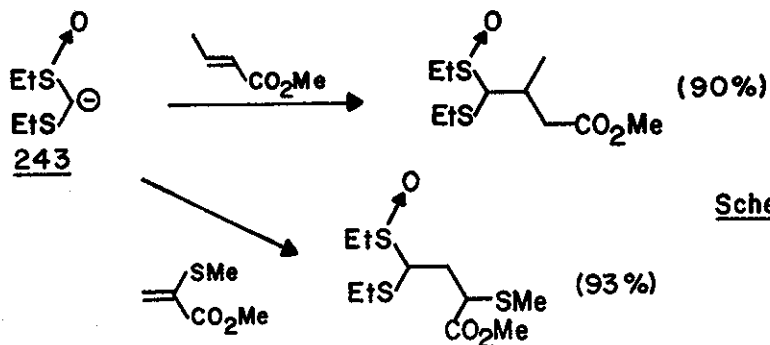
The unsubstituted anion 271 was also found to undergo conjugate addition



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

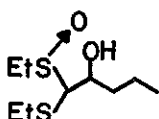
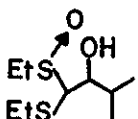
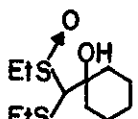
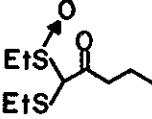
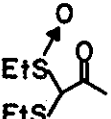
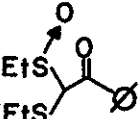


Scheme 8

The anion 271 undergoes smooth 1,2-addition to aldehydes, ketones, esters, and acid chlorides⁸⁸. 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

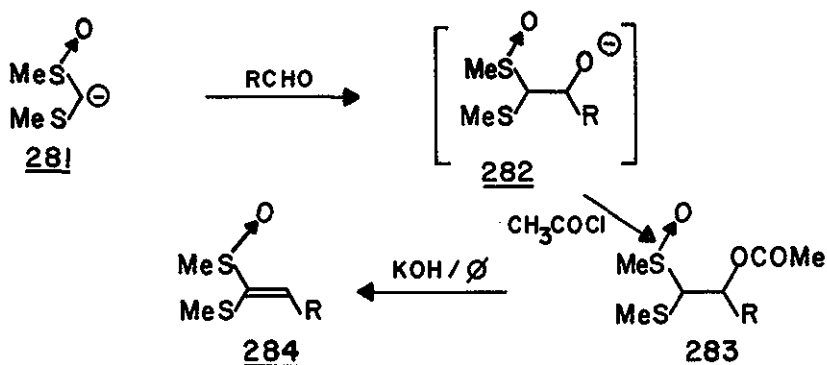
Products from the condensation of aldehydes, ketones, esters, and acid chlorides with the thioacetal monosulphoxide anion 271

<u>Carbonyl Compound</u>	<u>Adduct</u>	<u>Yield</u>
<chem>CCCC=O</chem>		95%
<chem>CC(C)C=O</chem>		97
<chem>C1CCCCC1=O</chem>		96
<chem>CCCC(=O)OCC</chem>		90
<chem>CC(=O)Cl</chem>		92
<chem>ClC(=O)Cl</chem>		90

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

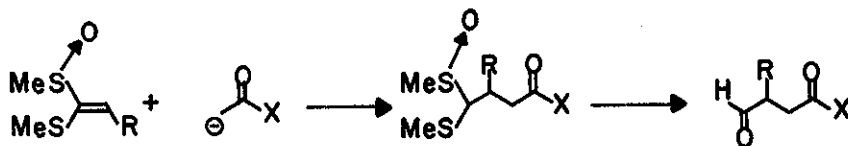
For substituted analogues of the anion, the reaction still proceeds in high yield with aldehydes and acid chlorides, but esters and ketones react only sluggishly.

Reaction of 281 with an aldehyde yielded the anion 282, which was quenched with acetyl chloride, forming the ester 283⁸⁸. On refluxing this compound in potassium hydroxide-benzene, elimination to the ketene thioacetal monosulphoxide 284 occurred. These compounds were used as 2-carbon Michael receptors⁹⁰, 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 11

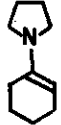
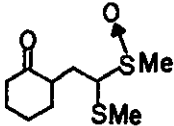

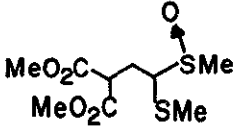
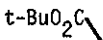
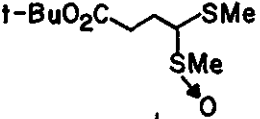
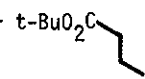
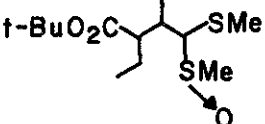


of compounds: enamines, sodium enolates derived from β -dicarbonyl compounds (or other compounds capable of generating a doubly stabilized anion), and

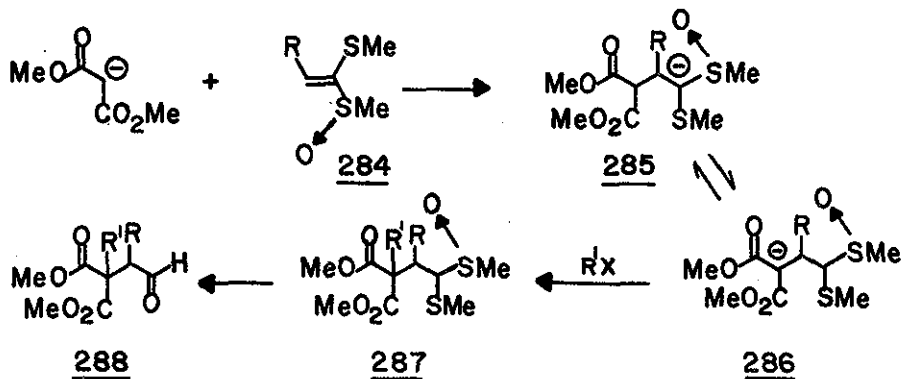
lithium enolates derived from simple ester systems. Some examples and the corresponding yields can be found in Table 25.

Table 25

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

Reactants	Product	Yield
<u>284</u> , R=H + 		92%
<u>284</u> , R=H + 		98
<u>284</u> , R=H + 		94
<u>284</u> , R=Me + 		90

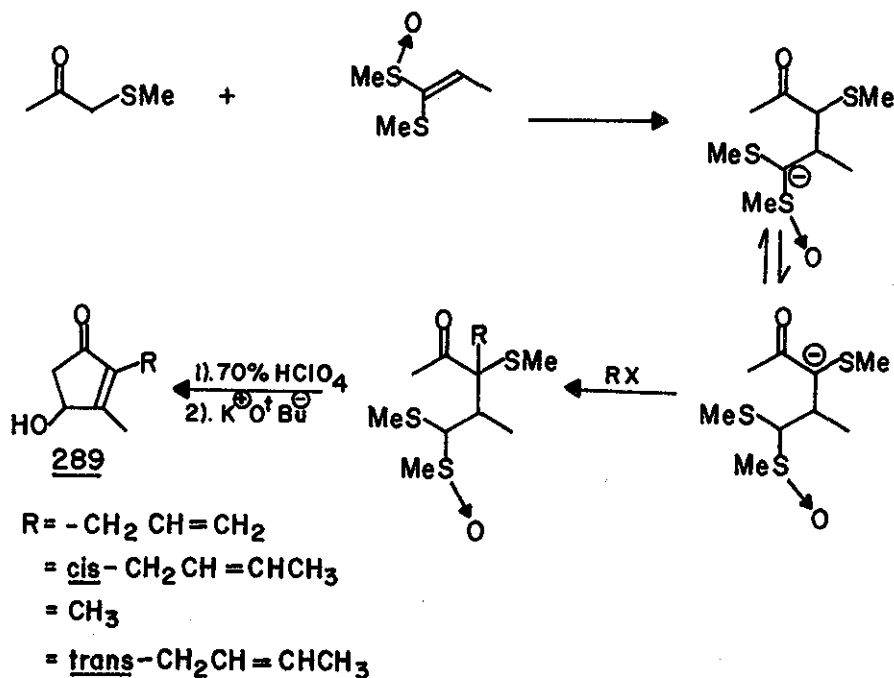
In the case of the reaction between 284 and β -dicarbonyl systems, the anion 285 was formed and then was equilibrated to 286⁹¹. Addition of an



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).

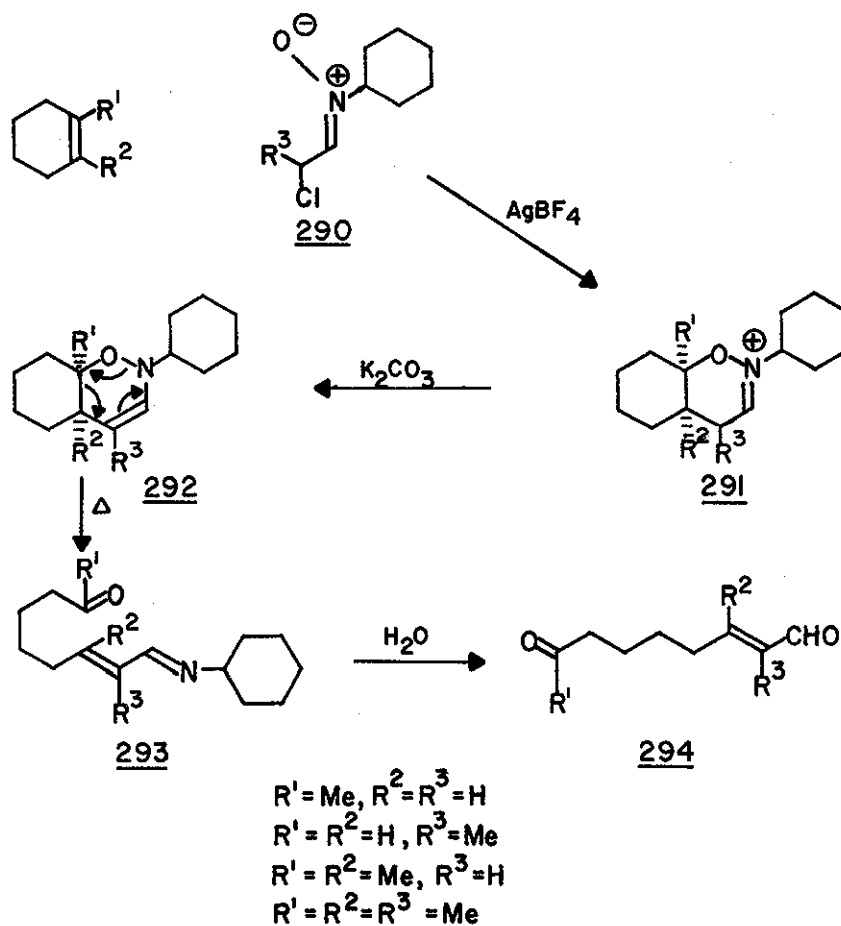
Scheme 12



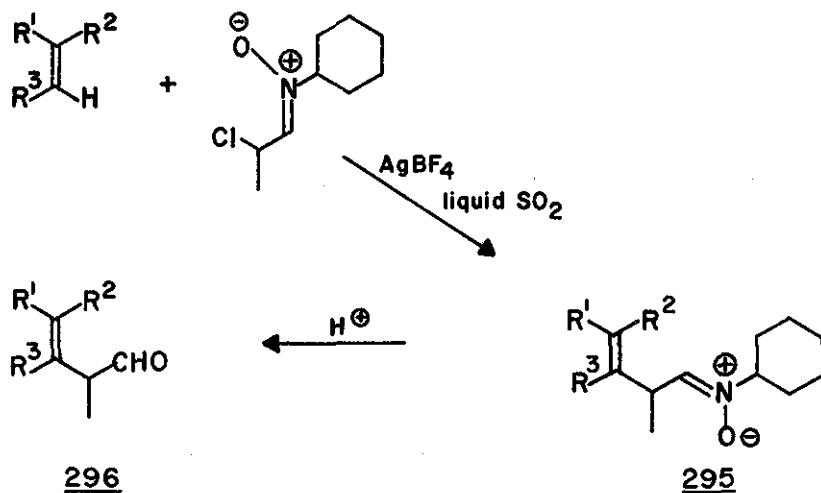
4) 1,2-Isioxazines

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 observed⁹⁵ rather than a cycloaddition process, affording **295**. The β,γ -unsaturated aldehyde **296** was isolated by acid treatment of **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 obtained⁹⁶ in 70 to 80 percent yield, presumably via the cyclic species 298 and 299.

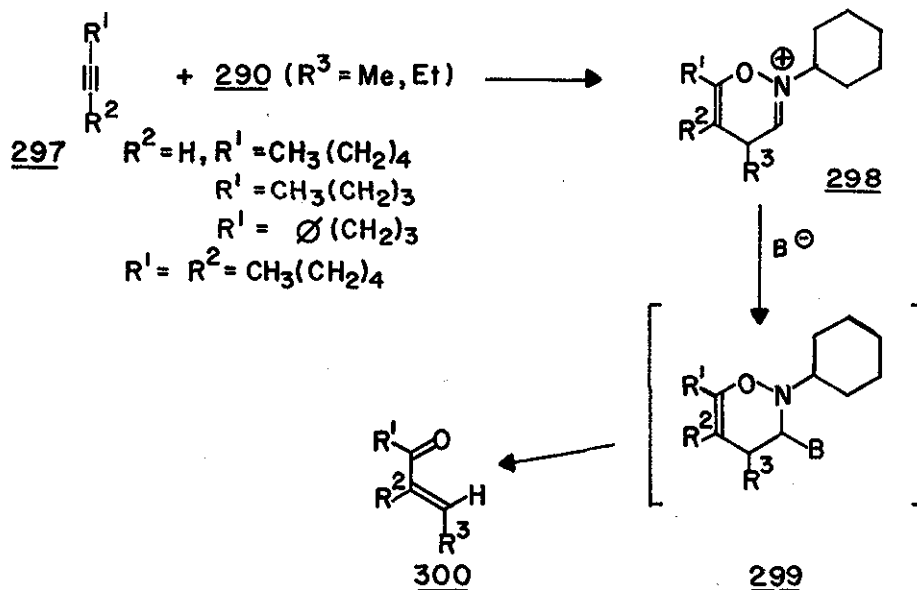

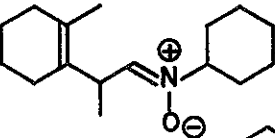

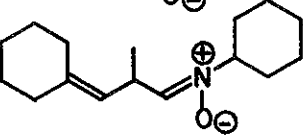

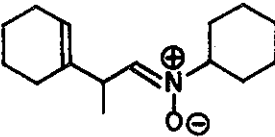

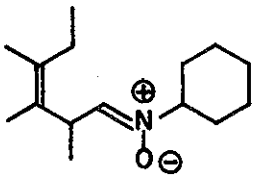
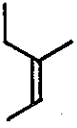
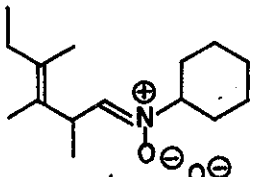
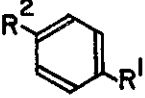
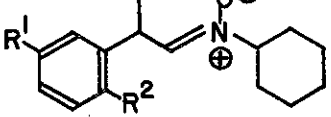


Table 26

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)	

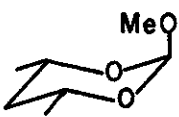
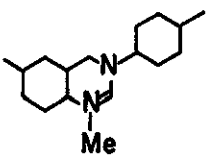
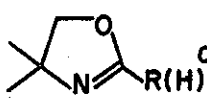
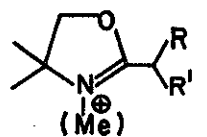
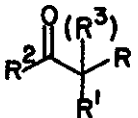
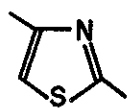
$R^1 = \text{OMe}, R^2 = \text{OMe}, \text{Me}$
 $R^1 = R^2 = \text{Me}$

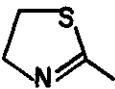
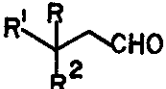
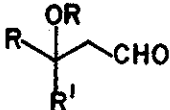
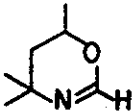
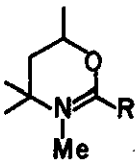
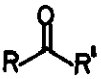
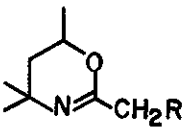
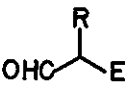
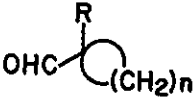
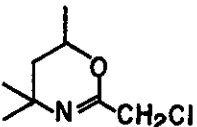
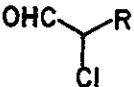
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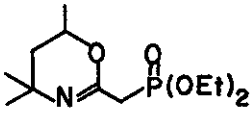
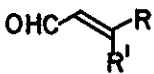
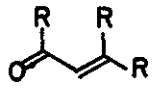
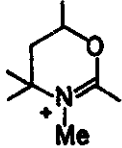
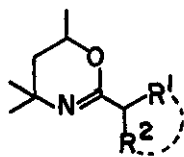
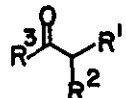
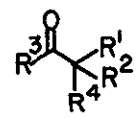
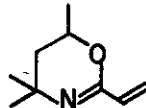
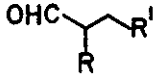
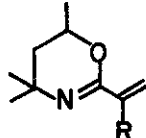
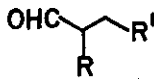
Rather than try to summarize in words the variety of carbonyl compounds available via the eleven heterocycles considered, the general structural features available from each one are presented in a table:

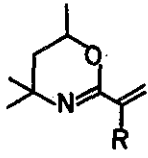


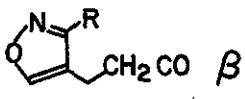
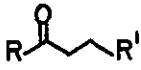




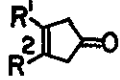
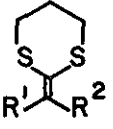
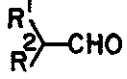
Table 27

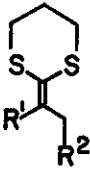
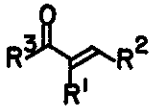
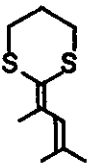
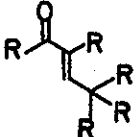
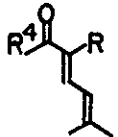
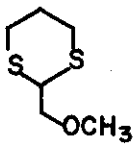


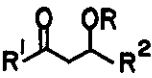
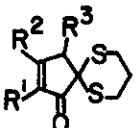
Structural features of carbonyl compounds available from the heterocyclic compounds discussed

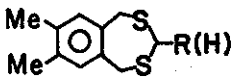
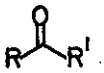
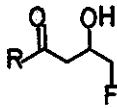

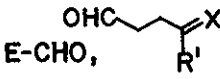

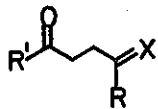
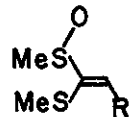
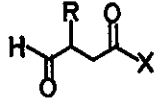
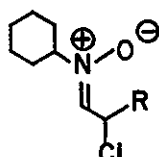
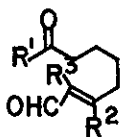
<u>Heterocycle</u>	<u>Alkylation Position</u>	<u>Other Positions</u>	<u>Product</u>	<u>Demasking Conditions</u>
	CARBONYL		RCHO	H ⁺
	CARBONYL		RCHO	H ⁺
	α (CARBONYL)		R-CHO	H ⁺
	CARBONYL	(α)		H ⁺
	α		E-CHO	NEUTRAL

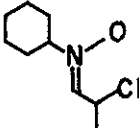
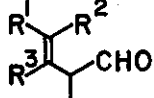
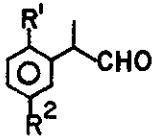
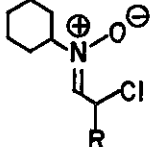
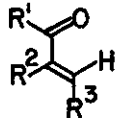
<u>Heterocycle</u>	<u>Alkylation Position</u>	<u>Other Positions</u>	<u>Product</u>	<u>Demasking Conditions</u>
	α			NEUTRAL
	α			NEUTRAL
	CARBONYL		RCHO	H^{\oplus}
	CARBONYL			H^{\oplus}
	α			H^{\oplus}
	α			H^{\oplus}
	α			H^{\oplus}

<u>Heterocycle</u>	<u>Alkylation Position</u>	<u>Other Positions</u>	<u>Product</u>	<u>Demasking Conditions</u>
	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}

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

<u>Heterocycle</u>	<u>Alkylation Position</u>	<u>Other Positions</u>	<u>Product</u>	<u>Demasking Conditions</u>
	CARBONYL			NEUTRAL, H ⁺
	γ	CARBONYL		NEUTRAL, H ⁺
	CARBONYL			NEUTRAL, H ⁺
	α	CARBONYL		NEUTRAL, H ⁺
	CARBONYL			NEUTRAL
	CARBONYL			

<u>Heterocycle</u>	<u>Alkylation Position</u>	<u>Other Positions</u>	<u>Product</u>	<u>Demasking Conditions</u>
	CARBONYL			NEUTRAL
				NEUTRAL
	CARBONYL			H [⊕]
	CARBONYL			H [⊕]
	CARBONYL			H [⊕]
	α			H [⊕]
	α			NEUTRAL

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

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