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α-OXO KETENE DITHIOACETALS AND RELATED COMPOUNDS: VERSATILE THREE-CARBON SYNTHONS

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1. INTRODUCTION

α-Oxo ketene dithioacetals[1] (1) have been known since 1910[2] and the n-butylthiomethylene functionality[3] (2) was introduced in 1959 as a protecting group for a methylene unit adjacent to a ketone functionality. The α-oxo ketene dithioacetal functionality can be viewed from several different perspectives. It is essentially a β-keto ester in which the ester functionality is protected as a ketene dithioacetal. Alternatively, it may be viewed as an α,β-unsaturated ketone containing a highly functionalized β-C atom. The vinylogous thiol ester functionality can be viewed in an analogous

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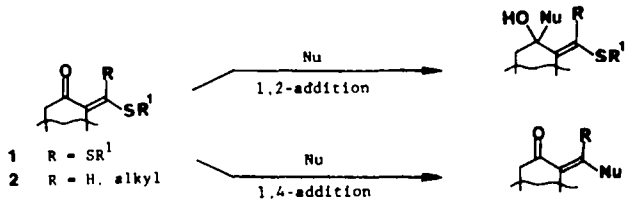
manner with the exception that the β-C atom is at a lower level of oxidation. From either perspective, these functionalities possess considerable potential for the regioselective construction of new bonds via 1,2-nucleophilic additions to the ketone carbonyl (Eq. 1) or 1,4-conjugate addition reactions to the β-C of the enone system (Eq. 2). The intermediate allylic alcohols and enones can, in turn, be exploited in additional bond forming transformations. Such reactivity patterns can also be exploited in other carbonyl conjugated ketene dithioacetals derived from esters, lactones, and active methylene compounds. Although the vinylogous thiol ester functionality has been primarily used as a protecting group, the α-oxo ketene dithioacetal functionality has received considerable attention as a versatile three-carbon fragment for heterocyclic synthesis. These heterocyclic syntheses generally exploit both the 1,2- and 1,4-nucleophilic addition reactions separately or sequentially in a cascade.



eq. 1

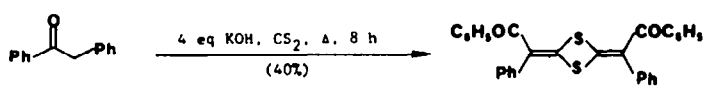
eq. 2

Prior to our work, many of the synthetic procedures were one-pot operations in which little opportunity was available for effecting controlled utilization of the functional group. We began an investigation of α-oxo ketene dithioacetals in 1980 with the aim of developing procedures for separating the two reactivity patterns and exploiting them in a sequentially controlled fashion. It was anticipated that such a strategy would provide considerable potential for the chemo-, stereo-, and regioselective construction of new bonds, particularly C—C bonds. Representative reactions illustrating the two principal reactivity modes of these functional groups will be described separately since they are the pivotal points for much of the chemistry devoted to synthetic applications. The extended application of this chemistry to the synthesis of heterocyclic compounds will then be described according to groups of heterocyclic systems. Although the chemistry of vinylogous thiol esters and α-oxo ketene dithioacetals has not been reviewed separately, fragments of information about these compounds have appeared in several review articles and monographs devoted to various aspects of organosulfur chemistry.[4]

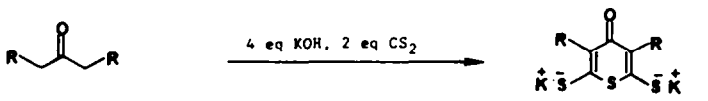
2. SYNTHESIS AND PROPERTIES

2.1. *Synthesis of β,β-bis(alkylthio)-α,β-enones and enoates*

The reactions of ketones and active methylene compounds with carbon disulfide in the presence of hydroxide and alkoxide bases has been known since 1891 when Meyer and Wege[5a] reported the preparation of the desaurins by treatment of ketones with carbon disulfide and powdered NaOH (Eq. 3[7a]). Related compounds had been prepared in 1877 by Norton and Oppenheim[6] by reaction of ethyl acetoacetate with CS_2 and zinc or lead oxide. Kelber and Schwarz later obtained the same compounds by heating bis-(S-benzoyl) derivatives of α-oxo ketene dithioacetals.[2c] The structures of these compounds were later confirmed by Yates *et al.*[7] Apitzsch, however, reported in a series of papers[8] that treatment of a ketone containing two adjacent methylene groups with potassium hydroxide and carbon disulfide afforded salts having the 1,4-thiopyrone structure (Eq. 4). In a later investigation, Wertheim[9] was unable to obtain thiopyrones from acetone under the same reaction conditions.



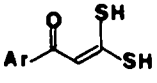
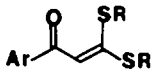
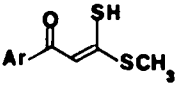
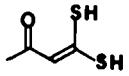
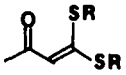
eq. 3



eq. 4

The first synthesis of an α-oxo ketene dithioacetal was reported in 1910 by Kelber and co-workers[2] and was obtained by alkylation of β-oxo dithioic acids with alkyl halides under basic reaction conditions. The β-oxo dithioic acids, however, were obtained in poor yields by reaction of an aryl ketone with CS_2 and KOH at 100° followed by neutralization with sulfuric acid (Table 1). Subsequent workers[10,11] were able to obtain good yields of the β-oxo dithioic acids from simple ketones by employing milder reaction conditions and the dithioic acids were converted to α-oxo ketene dithioacetals employing procedures similar to those of Kelber and co-workers (Table 1). The stability of the dithioic acids is dependent upon substrate structure and those derived from active methylene compounds generally display greater instability.[4b,11] In these instances, stable dithioate esters can be

Table 1. Synthesis of β-keto dithioic acids, β-keto dithio esters, and α-oxo ketene dithioacetals

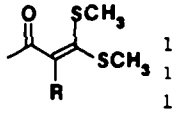
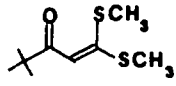
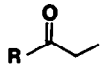
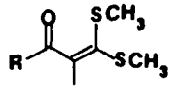
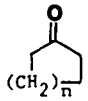
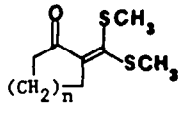
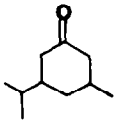
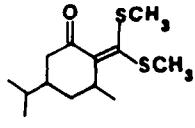
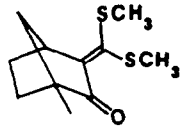
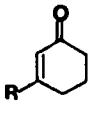
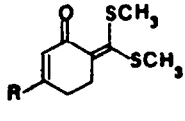
Ketone	Rxn Cond	Dithioic Acid % Yield	Rxn Cond	Electrophile R-X	Dithio Ester or Dithioacetal % Yield	Ref
						
Ar = Ph	A	20	1	CH_3X, $PhCH_2X$ $PhCOCl$, $X(CH_2)_2X$ $X(CH_2)_3X$		2a-b
	B	84	1	CH_3X, $PhCH_2X$ $X(CH_2)_2X$		10a
						
	C	90	2	MeI	46	11
p-MeC_6H_4	B	86				10a
	C	79	2	MeI	39	11
p-$MeOC_6H_4$	B	84				10a
	C	93	2	MeI	55	11
p-ClC_6H_4	B	92				10a
	C	83	2	MeI	72	11
			2	n-PrI	59	11
			2	EtO_2CCH_2Cl	61	11
			2	$MeO_2CCH_2CH_2Br$	59	11
p-PhC_6H_4	B	76				10a
	C	65				11
p-$MeCOC_6H_4$	C	6				11
p-NCC_6H_4	C	2				11
2-thienyl	A	65				2b
	C	93				11
						
	B	100	1	MeX	74	10b
				EtX	40	10b
				$PhCH_2X$	17	10b
				$CH_2=CHCH_2X$	43	10b
				$X(CH_2)_2X$	37	10b
				$X(CH_2)_3X$	15	10b

[a] A = KOH, H_2O, CS_2, 100°C. B = 2N sodium tert-amylate, PhH, CS_2. C = potassium tert-butoxide, Et_2O, CS_2. [b] 1 = MeOH, NaOMe, RX. 2 = n-Bu_4NOH, H_2O, $CHCl_3$, RX.

isolated by monoalkylation, although the nature of the base and counter ion appear to have an effect on the alkylation process[12] (*vide infra*).

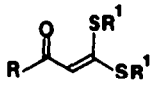
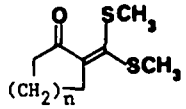
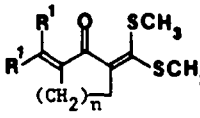
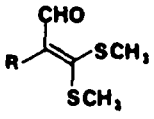
In the early 1960s Thuillier and Vialle investigated the chemistry of α-oxo ketene dithioacetals and found that they could be prepared directly from ketones (Table 2) in good yields by using sodium t-amylate as the base and two equivalents of an alkyl halide.[13] Later workers introduced lithium 2,6-di-t-butyl-4-methylphenoxide[14] and lithium dialkylamide bases.[15] Utilization of lithium dialkylamide bases, however, generally requires the sequential introduction of reagents since they readily add to CS_2 to afford dithiocarbamates after alkylation.[15c] The use of NaH was also investigated, but this base afforded low yields of α-oxo ketene dithioacetals from aliphatic ketones (23–45%) and when used with esters gave substantial amounts of Claisen condensation products.[16] Good yields of α-oxo ketene

Table 2. Synthesis of α-oxo and α-formyl ketene dithioacetals

Substrate	R or n	Rxn Cond	Electrophile R^1-X	% Yield	Product	Ref
	Me	A	CH_3I	72		13a
	n-Pr	A		62		13a
	n-Bu	A		92		13a
	Ph	A		64		13a
		A	CH_3I	65		13a
		B		45		16
	i-Pr	A	CH_3I	47		13a
	Et	A		61		13a
		B		30		16
		C		81		15c
	1	A	CH_3I	65		13b
	2	A		72		13b
		B		23		16
		C		84		15c
		D		86		14
	3	A		65		13b
	4	A		65		13b
		A	CH_3I	90		13b
		A	CH_3I	37		13b
	H	C	CH_3I			31
	Me	C				30
	i-PrO	C		80		15c

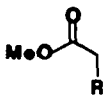
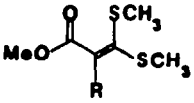
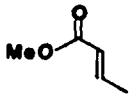
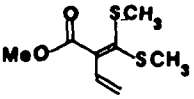
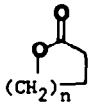
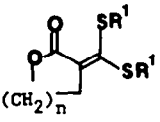
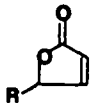
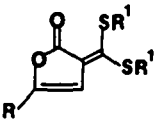
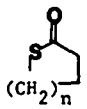
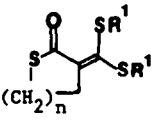
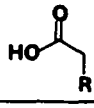
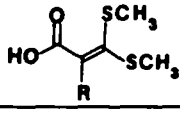
dithioacetals were obtained with NaH and CS_2 from aromatic ketones (60–90%) and several workers have effectively employed this combination (in PhH, DMF, or DMSO) for the synthesis of conjugated ketene dithioacetals from aryl and heteraryl ketones[17–19] and active methylene compounds.[20–23] Potassium t-butoxide (in PhH, DMF, or PhH/DMF) is also an effective base[10a,24–28] and a K^+ t-BuO^-/THF/CS_2/RX combination has recently been developed as a particularly effective procedure[29] for generating α-oxo ketene dithioacetals. The use of strong amide bases opened the way for the synthesis of conjugated ketene dithioacetals from a variety of enolate anions such as α,β-enones (Table 2),[15c,30,31] esters,[15a,c] lactones,[15c] and α,β-unsaturated esters (Table 3),[15c] and from nitriles,[15c] and hydrazones.[15c] Conjugated ketene dithioacetals had previously been prepared in good yields from lactones[32a] and thiolactones[32b] with sodium t-amylate in benzene. These procedures were also

Table 2—*Continued*

Substrate	R or n	Rxn Cond	Electrophile R^1-X	% Yield	Product	Ref
	Ph	E	CH_3I	58		17b
	4-$MeOC_6H_4$	E		61		17b
		B		80		16
	2-pyridyl	E		71		17b
	2-furyl	E		44		17b
		F		95		19
	2-thienyl	E		68		17b
		F		91		19
		F	NH_2COCH_2X	94		19
	6-Br-2-pyridyl	E	CH_3I	66		17b
	5-Br-2-thienyl	E		73		17b
	2-ClC_6H_4	F		87		18
		F	$PhCH_2Br$	45		18
	2,5-$Cl_2C_6H_3$	F	CH_3I	89		18
		F	$PhCH_2Br$	36		18
	1	A	CH_3I	84		13b
			EtI	60		13b
	2	A	CH_3I	86		13b
			EtI	66		13b
	3	A	CH_3I	51		13b
	4	A		38		13b
	Ph	F	CH_3I	50		40
	4-$MeOC_6H_4$	F		41		40
	4-MeC_6H_4	F		59		40
	2-MeC_6H_4	F		55		40
	Et	G		15		40
		H		45		31

[a] A = i. sodium tert-amylate, CS_2 ii. RX. B = NaH, PhH, CS_2, RX. C = i. LDA (or LHMDS), HMPA ii. CS_2 iii. LDA (or LHMDS), THF iv. RX. D = lithium 4-methyl-2,6-di-tert-butylphenoxide, Et_2O, CS_2, RX. E = NaH, PhH (or $PhCH_3$), 5% v/v N,N-dimethylacetamide, RX. F = NaH, DMSO, RX. G = i. sodium tert-amylate, Et_2O, -20°C, CS_2 ii. RX. H = KH, THF, CS_2, RX.

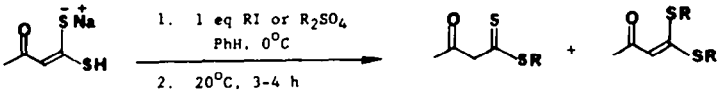
Table 3. Synthesis of conjugated ketene dithioacetals from esters, lactones, thiolactones, and carboxylic acids

Substrate	R or n	Rxn Cond	Electrophile R^1-X	% Yield	Product	Ref
	C_7H_{15}	A	CH_3I	78		15a
	$C_{14}H_{29}$	A		58		15a
	$PhCH_2$	B		80		16
		C		29		15c
		D		71		15c
	1	C		37		15c
		D		81		15c
		E		75		32a
		E	$Br(CH_2)_2Br$	28		32a
	3	E		44		32a
		B	CH_3I	60		32a
	Me	E		43		32a
		E	$Br(CH_2)_2Br$	11		32a
	Ph	B		92		32a
		E	CH_3I	4		32a
		B		94		32a
	1	E	CH_3I	75		32a
		E	$Br(CH_2)_2Br$	19		32a
	2	E		38		32a
		E	CH_3I	68		32a
	C_7H_{15}	F	CH_3I	40		15a
	$C_{14}H_{29}$	F		56		15a

[a] A = i. LDA, HMPA, THF ii. CS_2 iii. n-BuLi iv. RX. B = NaH, CS_2, RX. C = i. LDA, HMPA, THF ii. CS_2 iii. LDA, THF iv. RX. D = i. LHMDS, HMPA, THF ii. CS_2 iii. LHMDS, THF iv. RX. E = sodium tert-amylate, PhH, CS_2, RX. F = i. LDA, HMPA, THF, 35°C, 30 min. ii. CS_2 iii. n-BuLi, -50°C iv. RX.

extended to the preparation of conjugated ketene dithioacetals[4b] from active methylene compounds (Table 4) such as malononitrile,[33] cyano ketones,[21-23,33f] cyano acetates,[12a,33a-d,f,34,35] cyano acetamides,[33a,c,d,f,34,35] β-keto esters,[12b,33f,36,37] β-diketones,[12b,33f,37,38] malonic esters,[12a,33f,37] and heterocyclic acetonitriles.[39] Conjugated ketene dithioacetals have also been prepared from nitriles,[15c,33a,b,34,35] nitromethane,[35] aldehydes,[31,40] and phenols.[41] Although, these procedures appear to be relatively straightforward, there are several difficulties that are frequently encountered.

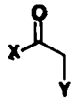
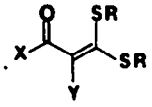
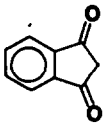
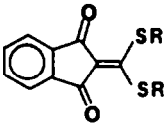
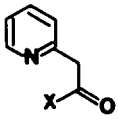
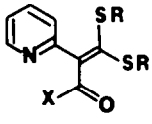
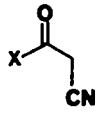
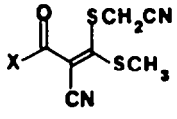
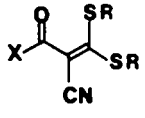
Although thiolate anions derived from the addition of enolate anions to CS_2 can be alkylated with one equivalent of an alkyl halide to afford dithio esters, a mixture of the ester and ketene dithioacetal is generally obtained (Eq. 5[10b]).[12a] The over alkylation reflects the nucleophilicity of sulfur centers and the



R = Me	64%	16%
R = Et	42%	14%
R = $PhCH_2$	21%	17%

eq. 5

Table 4. Synthesis of conjugated ketene dithioacetals from active methylene compounds

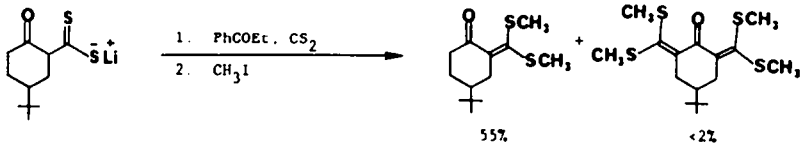
Substrate	X	Y	Rxn Cond	Electrophile R-X (R^1-X)	% Yield	Product	Ref
	MeO	CN	A	Me_2SO_4	87		34
			A(60°C)	$PhCH_2Cl$	90		34
	MeO	CO_2Me	A	Me_2SO_4	40		34
	Ph	CN	B	MeI	100		33f
		CO_2Et	B		60		33f
		COMe	B		13		33f
	Me	Ph	B		35		33f
		COMe	B		59		33f
		CO_2Me	B		42		33f
			C	Me_2SO_4	60		38
			D	EtO_2CCH_2X	25		38
			D	$PhCOCH_2X$	22		38
			D	$X(CH_2)_2X$	48		38
			D	$X(CH_2)_3X$	50		38
	Ph		E	CH_3I	62		20
			E	$Br(CH_2)_2Br$	46		20
			E	$Br(CH_2)_3Br$	96		20
	2-furyl		E	CH_3I	30		20
	i-Bu		E	$Br(CH_2)_3Br$	92		20
	i-Pr		E	$Br(CH_2)_3Br$	83		20
	Ph		E	$CH_3I(ClCH_2CN)$	66		21
	p-ClC_6H_4		E		80		21
	3,4-$Cl_2C_6H_3$		E		45		21
	2-thienyl		E		91		21
	Ph		E	CH_3I	87		23
			E	$X(CH_2)_2X$	91		23
			E	$X(CH_2)_3X$	64		23
			E	$PhCH_2$	88		23
	p-ClC_6H_4		E	CH_3I	60		23
			E	$X(CH_2)_2X$	42		23
			E	$X(CH_2)_3X$	38		23
	2-furyl		E	CH_3I	75		23
			E	$X(CH_2)_2X$	69		23
			E	$X(CH_2)_3X$	73		23
	2-thienyl		E	CH_3I	46		23
	1-cyclohexyl		E	CH_3I	69		23

[a]A = NaOMe, MeOH, CS_2, RX. B = PhH, DMF, NaH, CS_2, RX. C = NaOH, DMF, CS_2, RX. D = DMF, sodium tert-amylate, CS_2, RX. E = NaH, DMSO, CS_2, RX.

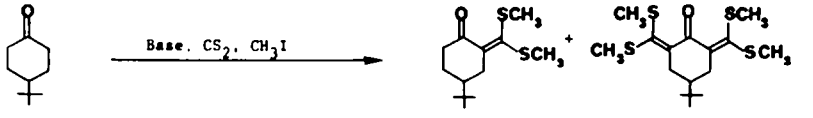
facility for proton transfer in these systems. Utilization of the n-Bu_4N^+ counter ion in an ion pair extraction technique afforded cleaner reactions giving β-oxo dithio esters in relatively good yields.[11] The n-Bu_4N^+ thiolate salts (monoanion) of active methylene compounds were reported to afford the corresponding dithio esters and ketene dithioacetals in a 2:1 ratio, although these results are ambiguous since excess alkylating agent was employed.[12b] Alternatively, good yields of dithio esters can be obtained by converting the enolate/CS_2 adduct into the dithiolate dianion with a second equivalent of base and quenching the dianion with one equivalent of an alkyl halide.[12a,23,42] Here, the

sulfur center in the dianion is more nucleophilic than the sulfur center in the monoanion or neutral dithio ester and chemoselective monoalkylation can be achieved.

The facility for proton transfer and sulfur alkylation was elegantly examined by Quiroga and co-workers.[15b] In this work they showed that treatment of a ketone with one equivalent of base, CS_2, and two equivalents of methyl iodide afforded high yields of α-oxo ketene dithioacetals resulting from a facile alkylation of the neutral S atom in either the thiocarbonyl or tautomeric thiol form. To demonstrate the facility for proton exchange, the thiolate intermediate was treated with one equivalent of propiophenone and CS_2 to afford a mixture of products that could be rationalized in terms of acid–base equilibria (Eq. 6). The formation of the bis-ketene dithioacetal **4** was favored in less polar solvents (Eq. 7) and this was interpreted to reflect the stability of enolate **5** which is presumably formed to a smaller extent (Eq. 8) in THF and HMPT which enhance the formation of solvent separated ion pairs. However, NaH afforded higher yields of bis-ketene dithioacetal **4** though it should afford lower yields based upon the above argument. If the excess NaH was destroyed before the addition of methyl iodide, the formation of **4** was not observed in HMPT but became the principal product in THF. Lithium 2,6-di-t-butyl-4-methylphenoxide[14] was observed to give modest yields of **4** in Et_2O;[15b] better yields of mono-ketene dithioacetals were obtained when THF was employed as the solvent.[15c]

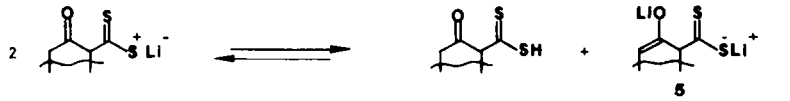


eq. 6



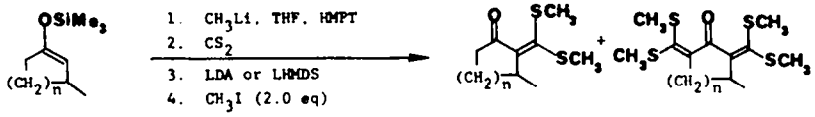
eq. 7

Base / Solvent	B / K / CS_2	Ratio 3 : 4	% Conversion
2,6-^{t}Bu$_2$-4-MePhOLi/Et_2O	2 / 1 / 5.3	60:40	98
LDA/Et_2O	2 / 1 / 5.3	75:25	78
LDA/THF	1 / 1 / 1.2	96:4	92
LDA/HMPT	1 / 1 / 1.2	100:0	82
NaH/HMPT	3.8/ 1 / 1.3	100:0	92
NaH/THF	3 / 1 / 3	15:85	98



eq. 8

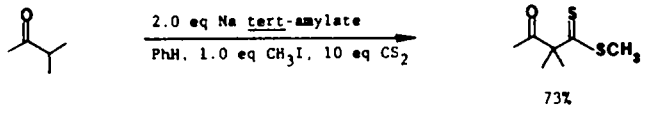
The facile acid–base equibria in these systems was readily apparent in the attempted preparation of regiospecifically substituted α-oxo ketene dithioacetals.[43,44] Treatment of the regiospecific enolate of 3-methylcyclopentanone sequentially with CS_2, one equivalent of LHMDS, and two equivalents of methyl iodide afforded the monoketene and bis-ketene dithioacetals in 75 and 12% yields, respectively (Eq. 9). Higher yields of the bis-ketene dithioacetal were obtained when LDA or higher reaction temperatures were used. The regiospecific enolate of 3-methylcyclohexanone, however, afforded the mono- and bis-ketene dithioacetals in 52 and 15% yields, respectively, when LDA was used as the base



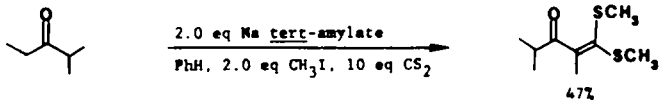
n	Base	Temp (°C)	% Yield		eq. 9
1	LHMDS	-78 to 0	75	12	
		25	40	27	
	LDA	-78 to 0	40	24	
2	LHMDS	-78 to 0	43	19	
		25	35	32	
	LDA	-78 to 0	52	15	

and higher yields of the bis-ketene dithioacetal were obtained with LHMDS and when higher reaction temperatures were employed. In these cyclic substrates, the steric hindrance of the 3-alkyl substituent undoubtedly decreases the rate of enolate–CS_2 alkylation and kinetic deprotonation. These results indicate that complex acid–base equilibria are occurring in these reactions and that the CS_2 alkylation step may be reversible.

In this regard, it is interesting to note that 2-methylcyclohexanone affords the α-oxo ketene dithioacetal when treated with two equivalents of 2,6-di-t-butyl-4-methylphenoxide in THF under equilibrium conditions or with LDA under kinetic conditions.[43,44] No β-keto dithio ester resulting from addition of the more substituted enolate anion to CS_2 was obtained. In contrast, Thuillier and Vialle reported[13a] that reaction of methyl isopropyl ketone with sodium t-amylate, CS_2, and methyl iodide in benzene afforded the dithio ester arising from reaction of the more substituted enolate anion with CS_2 (Eq. 10) while ethyl isopropyl ketone afforded the ketene dithioacetal under similar conditions (Eq. 11). In general, the equilibrium processes involved in the CS_2 alkylation of enolate anions derived from unsymmetrical ketones ultimately favors formation of the ketene dithioacetal by addition of CS_2 to the methylene group. Methyl ketones containing no adjacent methylene group appear to be an exception (Eq. 10) and this may reflect intermediate enolate stabilities.

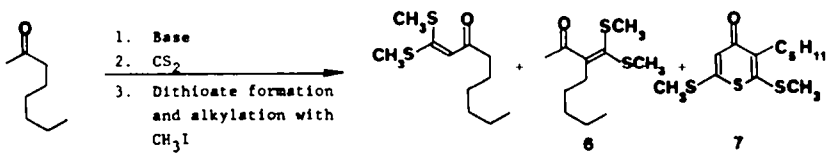


eq. 10



eq. 11

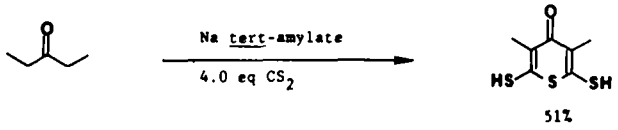
Reaction of methyl ketones with CS_2 and potassium t-butoxide, sodium t-amylate, or 0.9 equivalents of LHMDS under equilibrium conditions affords the ketene dithioacetal derived from the thermodynamically favored enolate (Eq. 12, Table 2).[44] Utilization of amide bases and CS_2 under kinetic conditions affords a complex mixture of products consisting of the ketene dithioacetals derived from the kinetic and thermodynamic enolates and the thiopyranone (Eq. 12). Although, this complication prevents the direct conversion of methyl ketones to the less substituted ketene



eq. 12

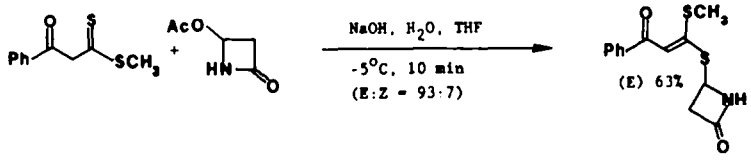
Base		% Yield	
2,6-^{t}Bu$_2$-4-MePhOLi	4	78	
0.9 eq LHMDS	22	59	
1.1 eq LHMDS	29	22	21

dithioacetal they can be readily prepared by an indirect method. This method involves the alkylation of 4,4-bis(methylthio)-3-buten-2-one which is readily prepared from acetone.[45a] Thiopyranone formation can become the principal reaction pathway under appropriate experimental conditions (Eq. 13).[10a,13a] Also, **6** was converted[44] into **7** by the procedure of Thuillier and Vialle. Reaction of acyclic α-oxo ketene dithioacetals with base, CS_2, and methyl iodide can give mixtures of α-oxo (bis)ketene dithioacetals and 2,6-dialkylthio-1-thia-4-pyranones.[13a]



eq. 13

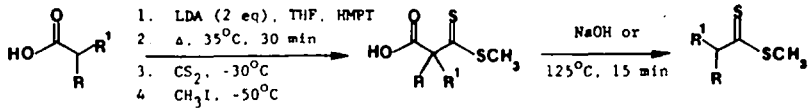
α-Oxo ketene dithioacetals, having two different alkylthio substituents, have also been prepared from β-oxo dithio esters by alkylation of the enolate with a different alkyl halide.[10b,11] Although an attempt was made to effect this alkylation stereoselectively by utilization of TlOEt in refluxing benzene[11] mixtures of *E* and *Z* stereoisomers were always obtained. Mixed alkylthio ketene dithioacetals were prepared stereoselectively by deprotonation and sulfenylation of vinylogous thiol esters with alkyl alkylthiosulfonates (Eq. 43).[46a] These compounds, however, were configurationally unstable and underwent isomerization upon attempted purification by silica gel chromatography. Sulfenylation of the vinyl anion with methylsulfinyl chloride afforded a 1:1 mixture of *E* and *Z* stereoisomers, a result suggesting a possible role of chloride ion in the isomerization process under the reaction conditions. Alkylation of β-oxodithio esters with 4-acetoxyazetidin-2-one afforded α-oxo ketene dithioacetals having two different alkylthio substituents stereoselectively and has potential utility in the synthesis of β-lactam antibiotics (Eq. 14).[47]



eq. 14

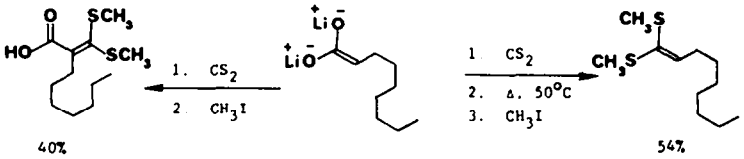
Aldehydes of the type, $ArCH_2CHO$, were converted into α-formyl ketene dithioacetals in moderate yields employing NaH in DMSO (Table 2).[40] Simple aliphatic aldehydes afforded low yields with the NaH/DMSO/CS_2/MeI combination but could be converted into α-formyl ketene dithioacetals in 40–50% yield with a KH/THF/CS_2/MeI combination.[31]

Although esters and lactones can be readily converted into the corresponding conjugated ketene dithioacetals, considerable difficulties are encountered with the carboxylic acids.[15a] The carboxylate dianions undergo a facile addition to CS_2, but the resultant 2-carboxydithioic acids obtained upon neutralization readily lose CO_2. This is in marked contrast to malonic acid derivatives. Alkylation on sulfur to afford alkyl 2-carboxydithio esters affords stable compounds that can be easily decarboxylated with NaOH or by heating (Eq. 15). Carboxylate dianions are converted into 2-carboxy ketene dithioacetals in poor to moderate yields. Heating of the CS_2 adduct results in decarboxylation to a dithiolate dianion which affords ketene dithioacetals upon alkylation (Eq. 16). Attempted

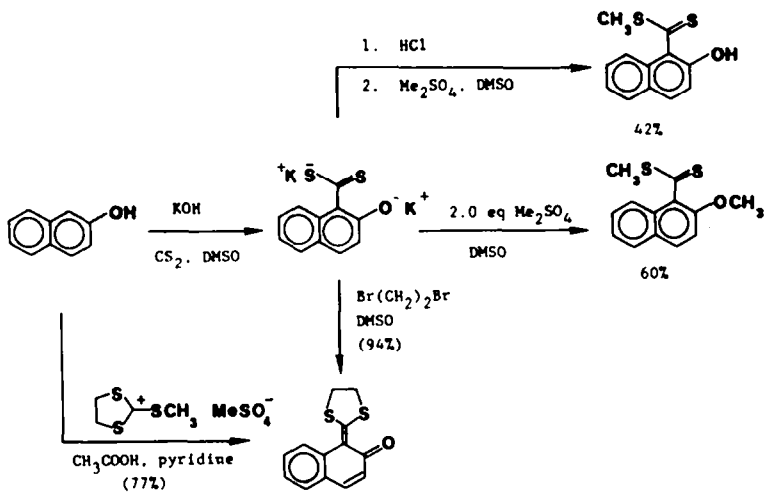


R	R^1	% Yield	% Yield
C_7H_{15}	H	88	65
C_7H_{15}	Me	77	69
$C_{14}H_{29}$	H	84	70

eq. 15



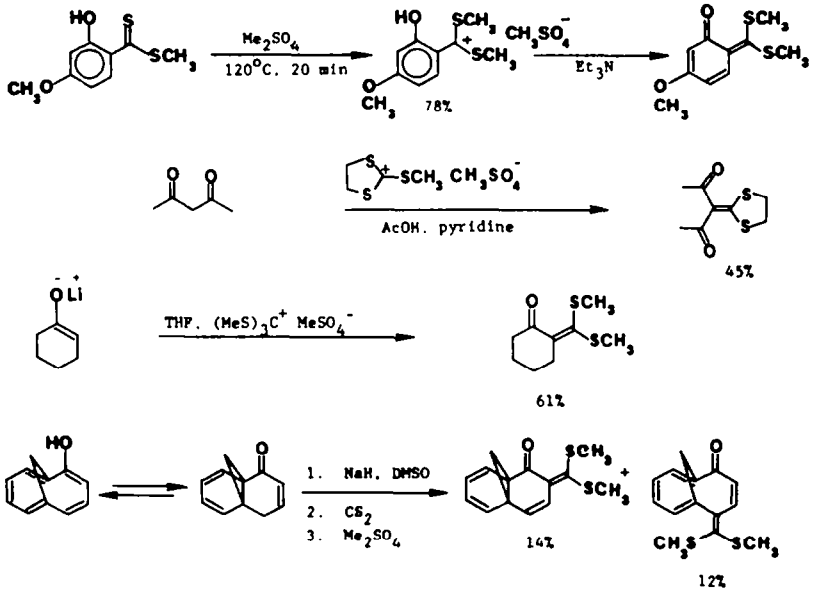
eq. 16



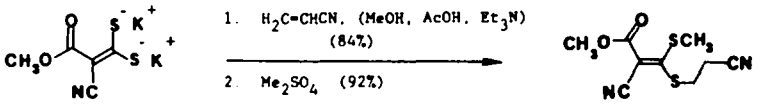
Scheme 1.

preparation of 2-carboxy ketene dithioacetals by alkaline hydrolysis of the corresponding 2-carboalkoxy derivatives has been reported by several authors to result in decarboxylation.[10b,15a,36]

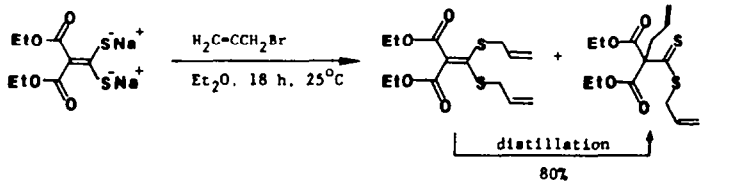
Phenols and naphthols have been converted into conjugated ketene dithioacetals under basic,[41] and acidic[48] reaction conditions. Reaction of phenols and naphthols with CS_2 and KOH readily afforded the salts of aryldithioic acids, although the products obtained upon alkylation of these salts were dependent upon the alkylating agent. Utilization of one and two equivalents of dimethyl sulfate afforded the hydroxyaryldithio esters and the methoxyaryldithio esters, respectively (Scheme 1).[41] Alkylation of the salts with 1,2-dibromoethane, however, afforded the ω,ω-bis(methylthio)quinone methides (Scheme 1). Phenols generally undergo CS_2 alkylation at the *para* position to afford *p*-hydroxyaryldithio esters. The hydroxyaryldithio esters can be alkylated to afford bis(methylthio) hydroxyaryl carbenium salts which readily afford the quinone methides upon treatment with base (Eq. 17).[41a,49] Hydroxyarylthio amides have been converted to quinone methides by a similar procedure.[48c] The quinone methides are generally unstable unless they contain bulky substituents and this procedure provides for an *in situ* generation of the compounds. The quinone methides can also be prepared from trithiocarbenium salts (Scheme 1) which have also been employed with active methylene compounds[48] (Eq. 18), nitroalkanes,[35] and thiolactones.[35] The trithiocarbenium salts also react with enolate anions to afford α-oxo ketene dithioacetals (Eq. 19) and this reaction may provide a solution to the problem of synthesizing regiospecifically substituted α-oxo ketene dithioacetals (*vide supra*).[50] Structurally intriguing α- and γ-oxo ketene dithioacetals have been obtained from conjugated cyclic $4n+2$ systems (Eq. 20).[51]



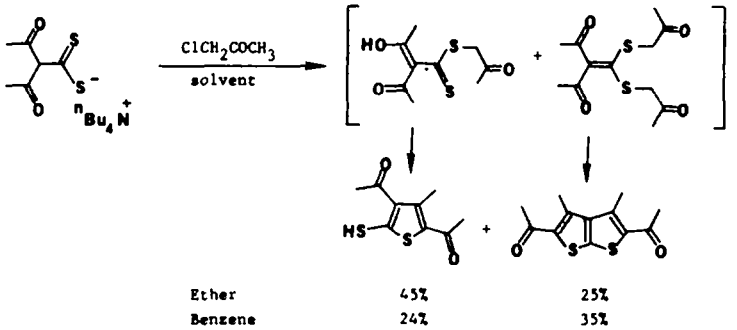
The dithiolate dianions derived from the addition of enolate anions to CS_2 can react on sulfur with a variety of electrophiles (Tables 1, 2 and 4). The sulfur acylation or alkylation has been achieved with acid chlorides,[2a,b,34] allylic halides,[11,12] propargyl halides,[11,12b] α-haloketones,[12b,21,38] α-haloesters,[11,21,38,52] α-halonitriles,[21,52] α-haloamides,[19,52] and α,β-unsaturated nitriles (Eqs 21–23).[35] The ketene dithioacetals derived from alkylation of sulfur with allylic and propargylic halides readily undergo thio-Claisen rearrangements (Eq. 22) while those derived from alkylation with α-halocarbonyl compounds undergo cyclization reactions under the basic reaction conditions (Eq. 23, *vide infra*).



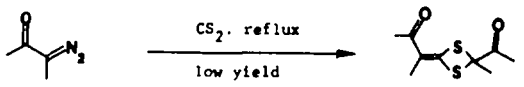
eq. 21



eq. 22

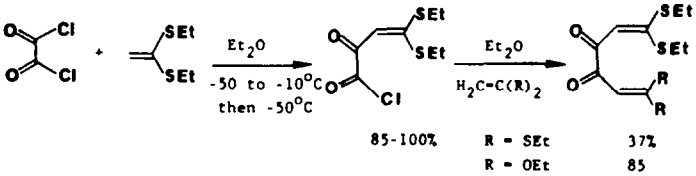


eq. 23

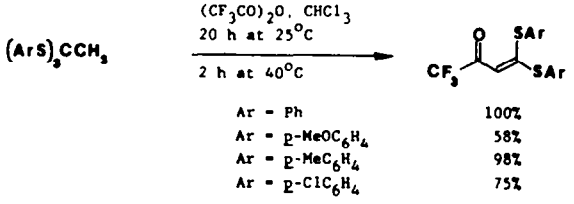


eq. 24

α-Oxo ketene dithioacetals have also been prepared by reaction of α-diazo ketones with CS_2[53] (Eq. 24) and by Friedel–Crafts acylation of ketene dithioacetals (Eq. 25[54a]).[4a,54] They have also been prepared by reaction of trithioorthoacetates with acylating reagents such as anhydrides and acid chlorides (Eq. 26).[55] The preparation of a sulfone conjugated ketene dithioacetal from a bis-carbanion

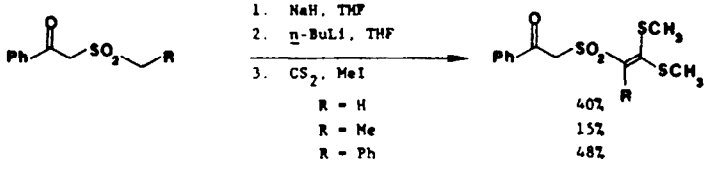


eq. 25



eq. 26

suggests interesting possibilities for extension to dicarbonyl compounds (Eq. 27).[56] Finally, the conjugated carboethoxy ketene dithioacetal, 1-[1-ethoxycarbonyl-2,2-bis(ethylthio)ethenyl]-2-ethylpyridinium iodide, has been prepared from 1-(ethoxycarbonylmethyl)-2-ethylpyridinium bromide[57] and exploited in a synthesis of a pyrano[2,3-b]indolizine containing an annulated α-pyrone ring.

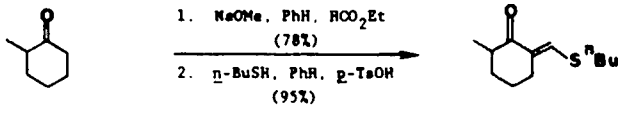


eq. 27

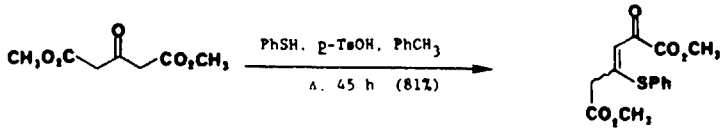
Although considerable difficulties can be encountered in the synthesis of conjugated ketene dithioacetals, many experimental conditions and strategies have been developed to overcome the problems. Even though enolate anions can be generated under kinetic or thermodynamic conditions and successfully alkylated with CS_2, satisfactory procedures still need to be developed to circumvent or prevent unfavorable equilibrium processes.

2.2. *Synthesis of β-alkylthio-α,β-enones and enoates*

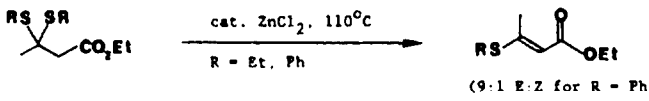
Vinylogous thiol esters are readily prepared by treatment of α-formyl ketones with a thiol in the presence of *p*-toluenesulfonic acid (Eq. 28).[3] This approach is useful for the preparation of vinylogous thiol esters from readily available α-formyl ketones and has been extended to β-keto esters (Eq. 29)[58–60] and symmetrical β-diketones[58] which afford β-alkyl-β-alkylthio-α,β-enones and enoates, respectively. β-Keto esters can be converted into β-thioxo esters[61] upon treatment with H_2S and these thiones should readily afford β-alkylthio-α,β-enoates upon sulfur alkylation. Reaction of β-keto esters with H_2S, however, sometimes affords the gem-dithio derivatives as the major product and this is especially true for acyclic β-keto esters containing an α-alkyl substituent. Although inconvenient, this is not a serious problem since β-alkylthio-α,β-enoates can be prepared by pyrolysis of the dithioacetals derived from β-keto esters (Eq. 30).[62] Vinylogous thiol esters can also be prepared from an intermediate tosylate for those compounds containing an acid sensitive functionality[3] and this procedure has been employed in the synthesis of β-arylthio-α,β-enoates from α-formyl esters (Eq. 31).[58] A variation of this procedure involves the substitution reaction of β-halo-α,β-enones and enoates with thiolate anions.[63]



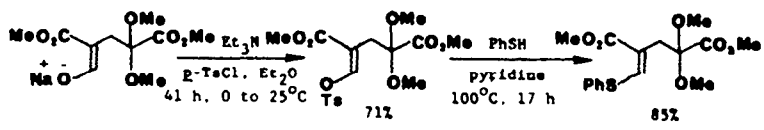
eq. 28



eq. 29



eq. 30

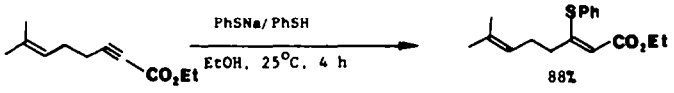


eq. 31

The reaction generally proceeds stereospecifically with retention of configuration, although mixtures of stereoisomers can be obtained. The reaction of β,β-dichloro-α,β-enones with thiolate anions has been exploited in the synthesis of vinylogous thiol esters, α-oxo ketene dithioacetals, and α-oxo ketene N,S-acetals.[64] Vinylogous thiol esters have also been prepared by acylation [$(CX_3CO)_2O$] of vinyl sulfides.[54b]

The synthesis of β-alkyl substituted vinylogous thiol esters from unsymmetrical β-diketones entails problems of regiochemistry and the best approach to these compounds involves the chemo-, and stereoselective reaction of organocuprates with α-oxo ketene dithioacetals (Eq. 81, Table 18).[46] The substitution reaction generally affords the *E* stereoisomer in a highly stereoselective fashion. The corresponding ester conjugated ketene dithioacetals do not undergo the substitution reaction unless an electron-withdrawing substituent is located at the α-position (Eq. 82). Vinylogous thiol esters containing no β-alkyl substituent can also be prepared from α-oxo ketene dithioacetals by reduction with $NaBH_4$ in the presence of $NiCl_2$ (Eq. 60).[65] Both *E* and *Z* stereoisomers are obtained as the predominant product depending upon the substrate structure (*vide infra*).

An alternative approach to β-alkyl-β-alkylthio-α,β-unsaturated carbonyl compounds involves the addition of thiols or their alkali salts to α-acetylenic ketones, esters, and carboxylic acids (Eq. 32).[46a,60,66,67,68a] Although the substitution generally proceeds with *trans* addition to afford the *Z*



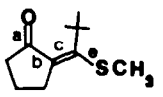
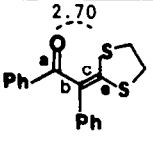
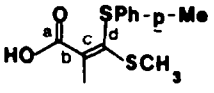
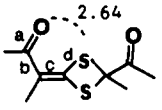
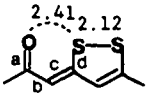
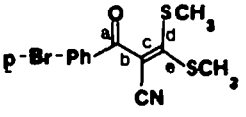
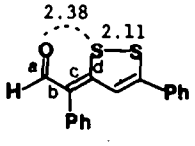
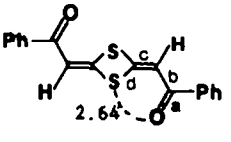
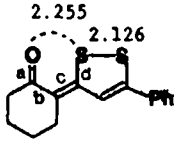
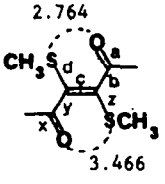
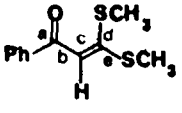
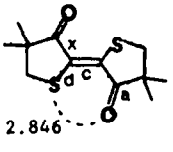
eq. 32

olefin, mixtures of stereoisomers are often obtained. The stereoselectivity of the addition appears to be dependent upon a number of structural features in the substrate and reaction conditions.[66a,67] Stereoconvergence is favored by low barriers to isomerization in the intermediate carbanion, formation of the allene enolate directly or competitively with carbanion protonation, and electrophile attack at the O atom. In this view,[66a] α-acetylenic ketones with low barriers to isomerization in the intermediate carbanion afford *trans* addition products in protic solvents and mixtures of stereoisomers in HMPT and DMSO in which the allene enolate is stabilized relative to the carbanion which is protonated slowly in these solvents. The former procedure generally gives the *Z* stereoisomers in a kinetically controlled process, although post isomerization events can also afford mixtures of stereoisomers.

2.3. *Physical properties*

Several X-ray diffraction studies have been done on α-alkylthio- and β,β-bis(alkylthio)-α,β-unsaturated carbonyl compounds (Table 5).[46a,69,70] In some instances, the S—O distance is shorter than the sum of the van der Waals' radii (3.25 Å) of sulfur (1.85 Å) and oxygen (1.4 Å) indicating a possible bonding interaction, although crystal packing forces may play an important role. The α-dithiolylidene ketones (isosteres of trithiapentalenes) also exhibit S—S bond lengths that are shorter than the sum of the van der Waals' radii for sulfur (3.7 Å) and longer than the covalent radii found in cyclic disulfides (2.0–2.1 Å).[70a] The X-ray data also reveal that the C—S bond *syn* to the carbonyl group is shorter than a normal C(sp^2)—S bond length of 1.75 Å and the C=C bonds are longer than the C=C bond of ethylene (1.34 Å). These structural parameters suggest a contribution from dipolar resonance forms such as **9** and **11**. Dipole moments, however, have been measured[70a,71] and the values (approx. 3–5 D), in comparison to the calculated value (13–20 D) for a fully ionic structure, are relatively small reflecting very minor contribution of zwitterionic resonance forms to the molecular structures. Although the σ and π contributions to the dipole moment cannot be separated experimentally, it has been argued[71] that the close agreement between measured and calculated (CNDO/2 method) values permits a reasonable estimate of the separate contributions. For the conjugated ketene dithioacetal of malononitrile the π polarization amounts to only 0.13 electrons. The bonding in the trithiapentalene[70a] analogs of **10** has been described as "no bond resonance" to indicate a delocalization of the electrons in the S—S σ-bond as indicated in resonance structures **13** and **14**. In the oxygen analogs (e.g. **10**) the S—S bond distance is "nearly" normal and molecular orbital calculations[72a] indicate that if there is any bonding attraction at all arising from the S···O overlap it is very small. Simple extended Hückel calculations yielded weakly S···O antibonding interactions which gave way to weakly bonding

Table 5. Bond lengths for β-alkylthio- and β,β-bis(alkylthio)-α,β-unsaturated carbonyl compounds

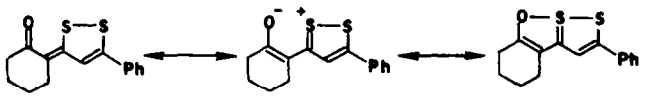
Cpd	Bond	Lengths (Å)	Ref	Cpd	Bond	Lengths (Å)	Ref
	a	1.219	46a		a	1.25	69
	b	1.481			b	1.49	
	c	1.358			c	1.38	
	e	1.763			e	1.72	
	a	1.214	69		a	1.27	69
	b	1.436			b	1.44	
	c	1.359			c	1.38	
	d	1.738			d	1.79	
	a	1.27	70a		a	1.212	69
	b	1.44			b	1.490	
	c	1.39			c	1.369	
	d	1.76			d	1.724	
					e	1.752	
	a	1.26	70a		a	1.27	69
	b	1.43			b	1.44	
	c	1.39			c	1.38	
	d	1.76			d	1.79	
	a	1.269	70a		a	1.218	69
	b	1.429			b	1.486	
	c	1.369			d	1.748	
	d	1.758			x	1.209	
					y	1.512	
					z	1.773	
	a	1.246	69		a	1.216	69
	b	1.440			c	1.372	
	c	1.378			d	1.735	
	d	1.745			x	1.484	
	e	1.748					

interactions when the calculations were carried out with an iterative adjustment of charges in the Coulomb integrals.[72a] Although these early results were independent of the d-orbitals, later investigations revealed their importance.[72b]

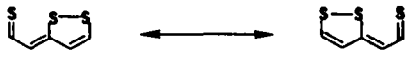
The extent and nature of the S···O interaction in these compounds is open to question, but the existence of some type of interaction is indicated by the IR and UV spectral properties of these compounds. The IR spectra of α-oxo ketene dithioacetals of type **15** show carbonyl absorptions around 1639 cm^{-1} while those of type **16** display absorptions around 1694 cm^{-1}.[7b,13a] In the latter compounds the steric interactions arising from the α-substitution causes the carbonyl group to twist out of the plane of the olefin resulting in loss of conjugation and a shift of the carbonyl frequency to higher wavenumbers. The intensities of the carbonyl group absorptions appears to be diminished relative to that for similar α,β-unsaturated enones. Although this phenomenon is generally true for the s-*cis* relative to the s-*trans* conformations, the reduction in intensity may reflect an interaction between the S and O atoms.[7b] The α-oxo ketene dithioacetals sometimes display split bands for the carbonyl and this splitting has been attributed to vibrational coupling with either the fundamental vibration of the olefin double bond or Fermi resonance. The latter coupling mechanism which involves overtone or combination vibrations is favored.[7b]

The vinylogous thiol esters can exist as stereoisomers with either the *E* or *Z* configuration about the

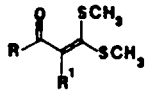
8 9



10 11 12

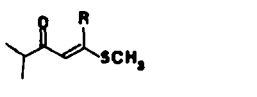


13 14

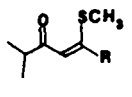


15 R = alkyl; R^1 = H
16 R = R^1 = alkyl

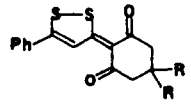
olefin double bond. These compounds display interesting spectral properties that can be exploited to assign olefin configuration. In the IR spectra,[46,60,63b,70b] the *Z* vinylogous thiol esters generally display carbonyl absorptions at lower wavenumbers than the corresponding *E* isomers (cf. **17** and **18**, Table 6). Interestingly, the carbonyl absorptions in **17** are shifted to lower wavenumbers as the steric bulk of the substituent increases while the carbonyl absorptions of **18** are shifted to higher wavenumbers.[46a] This trend indicates that the actual values for the carbonyl absorption may reflect both steric and electronic factors and this might account for those exceptions where the *E* isomer displays a carbonyl absorption at lower wavenumbers than the *Z* isomer. The effect of the S···O interaction on the carbonyl absorption is clearly illustrated by several α-(1,2-dithiol-3-ylidene)-β-diketones containing carbonyl groups *cis* and *trans* to the S atom (**19**, **20**).[70b] Again, the carbonyl *cis* to the S atom absorbs at lower wavenumbers and this difference diminishes in the 5-membered ring analog where geometry necessitates a larger internuclear separation. The *cis* and *trans* isomers **21** and **22** also display trends consistent with those observed for the simpler vinylogous thiol esters.[60] In a similar fashion, the *E* vinylogous thiol esters display a more intense UV absorption at shorter wavelengths than the corresponding *Z* isomers.[46a,60] Consequently, the intensity and wavelength dependence of the long wavelength UV absorptions parallel the IR carbonyl absorptions. This trend has been attributed to an S···O interaction in the *Z* isomer involving zwitterionic resonance contributors (e.g. **9** and **11**). However, both the *E* isomer **17c** (λ_{max} 297, 290, and 288 nm) and the *Z* isomer **18c** (λ_{max} 308, 302, 300 nm) display identical numerical shifts of λ_{max} as the solvent polarity is varied (along the series ethanol,



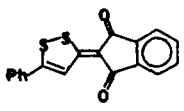
17 a R = CH_3
b R = n-Bu
c R = sec-Bu
d R = tert-Bu



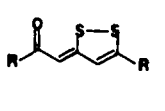
18



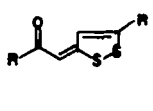
19 a R = H
b R = CH_3



20



21 a R = CH_3
b R = Ph



22 a R = CH_3
b R = Ph

Table 6. Carbonyl IR stretching frequencies for *cis* and *trans* γ-keto vinyl sulfide units

Compounds		trans-carbonyl KBr ν(CO) (solvent)		cis-carbonyl KBr ν(CO) (solvent)		Ref
17a	18a		1670 (CCl_4)		1647 (CCl_4)	46a
17b	18b		1663		1655	46a
17c	18c		1660		1660	46a
	18d				1673	46a
19a		1624	1643 ($CHCl_3$)	1547	1554 ($CHCl_3$)	70b
19b		1638	1646	1546	1558	70b
20		1680	1693	1637	1644	70b
21a	22a		1645 (C_2Cl_4)		1595 (C_2Cl_4)	70b
21b	22b		1635		1559	70b

ether, and hexane, respectively) reflecting no difference between the two isomers in terms of charge separation.[46a]

In the NMR spectra, the β-methyl, β-methylene, and γ-methine protons *syn* to the ketone carbonyl in the *E* isomers absorb downfield relative to those in the *Z* isomers in accord with the well-established trends for α,β-unsaturated carbonyl compounds.[46a] The structures and tautomeric ratios of β-thioxo ketones and esters have been investigated by several groups employing ^{1}H-NMR, IR, UV, Raman, and X-ray photoelectron spectroscopy.[73]

The stereochemistry of push–pull ethylenes has been reviewed[71] and barriers to rotation about the C=C bond have been measured for a number of β-alkylthio- and β,β-bis(alkylthio)-α,β-unsaturated carbonyl compounds (Table 7). Measurements were made by the dynamic NMR technique (DNMR) at the temperatures of coalescence and the energy barriers are expressed in terms of $\Delta G_c^{\ddagger}$ (Table 7). The DNMR method is applicable for a range of energy barriers between 6 and 25 kcal mol^{-1} (−140 to 200°). These energy barriers are a function of the acceptor and donor groups attached to the double bond and

Table 7. Rotational barriers for conjugated ketene dithioacetals determined by DNMR (abstracted from Ref. 71)

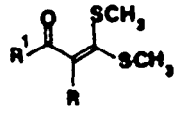
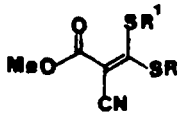
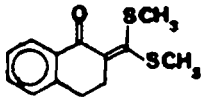
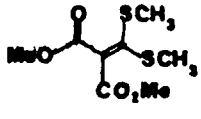
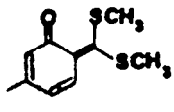
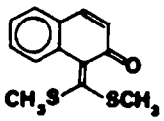
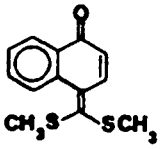
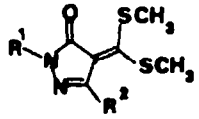
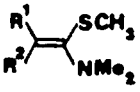
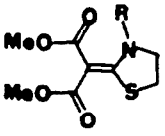
Compound	R^1	R^2	solvent[a]	$\Delta G^{\ddagger}$ (kcal/mol)	°K
	Me	H	ODC	25	470
	Me	Ph	ODC	25	470
	Ph	CN	ODC	20.6	398
	Ph	CO_2Et	ODC	19.4	375
	Ph	MeCO	ODC	18.0	353
	Me	Me	ODC	24.8	462
	$PhCH_2$	$PhCH_2$	ODC	24.7	455
	Me	$PhCH_2$	$CDCl_3$	22.4[b]	303
			ODC	22.9[b]	303
			ODC	23.3	440
			ODC	27.5	298
			CS_2	13.7	259

Table 7—*Continued*

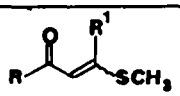
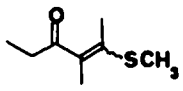
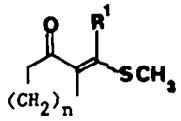
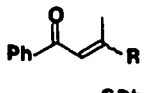
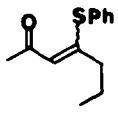
Compound	R^1	R^2	solvent[a]	$\Delta G^{\ddagger}$ (kcal/mol)	°K
			CS_2	7.8	160
			CS_2	8.2	170
	Me	Me	ODC	21.5	403
	Ph	Me	ODC	18.8	358
	Me	Ph	ODC	18.1	366
	Ph	Ph	ODC	16.2	328
	MeO_2C	CN	$CHCl_2F$	7.4	163
	Ph	MeCO	$CHCl_2F$	6.7	153
	MeCO	MeCO	$CHCl_2F$	<6	<130
	MeO_2C	MeO_2C	$CHCl_2F$	<6	<130
	H		PhMe	22.3	396
	Me		PhMe	<9.4	<137

[a]ODC = o-dichlorobenzene [b]By stereomutation

in general simple vinylogous thiol esters and α-oxo ketene dithioacetals have energy barriers greater than 25 kcal mol^{-1} which are not accessible by the DNMR method. The presence of two acceptor groups in several conjugated ketene dithioacetals derived from active methylene compounds lowers the energy barrier into the 18–22 kcal mol^{-1} range where isomerization can occur readily at room temperature. The quinone methide derivatives display low barriers to rotation indicative of the aromatic character of the zwitterionic transition state. The heterocyclic analogs display considerably higher barriers (16–21 kcal mol^{-1}) but generally lower than simple vinylogous thiol esters and α-oxo ketene dithioacetals. Carbonyl conjugated ketene N,S-acetals exhibit low energy barriers to rotation about the C=C bond unless H-bonding is present. The energy barriers for a series of compounds indicate the following order of donor capacity: H, OMe < MeS, MeS < H, NMe_2 < Me_3SiO, OMe < Me_2N, Me_2N < MeS, NMe_2. It has been noted, however, that the donor capacity is dependent upon the acceptor moieties and reversals of the above order may be observed. In a few instances $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values have been determined. Large negative entropies (−15 to −24 e.u. for conjugated ketene dithioacetals) were observed for the isomerization indicating increased polarity in the transition state which results in a more ordered solvated structure. The entropies became more negative with increasing solvent polarity as expected.

Although the barriers to rotation about the C=C bond of simple α-oxo ketene dithioacetals are generally not accessible at room temperature, attempts to prepare mixed alkylthio derivatives stereoselectively requires considerable care indicating that acid-catalyzed isomerization can occur quite readily.[11,46a] Presumably, protonation increases the acceptor capacity of the carbonyl and lowers the barrier to rotation.[71] Similarly, many of the vinylogous thiol esters are configurationally unstable in the presence of acids and several workers have examined the thermodynamic stability of the

Table 8. Thermodynamic stabilities of *E* and *Z* vinylogous thiol esters

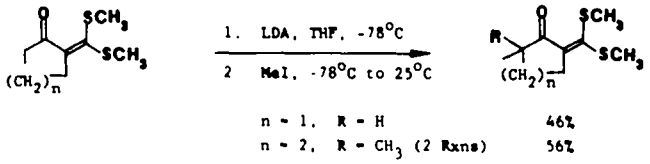
Substrate	R or n	R^1	E:Z	Ref
	Me	Me	73:27	46a
	Me	sec-Bu	82:18	46a
	i-Pr	sec-Bu	81:19	46a
			55:45	46a
	1	Me	84:16	46a
	2	Me	60:40	46a
	SEt		>95:5[a]	60
	SPh		>5:95[a]	63b, 60
	S(O)Et		>95:5[a]	63b, 60
			42:58	46a

[a]Estimated

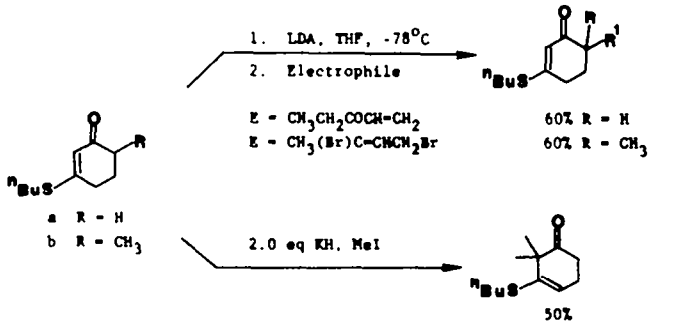
stereoisomers (Table 8).[46a,60,62b] Interestingly, arylthio derivatives appear to be more stable in the *Z* configuration while the alkylthio derivatives are more stable in the *E* configuration. This wide variation in isomer stability suggests competitive play of steric and electronic factors.

2.4. *Deprotonation*

α-Oxo ketene dithioacetals[13a,74] and vinylogous thiol esters[3,4f,68,75] can be readily deprotonated at the α′-position with strong bases. The resulting enolate anions can be alkylated with alkyl halides,[3,4f,74b,75] aldehydes,[13a,68,74a] or enones[75b] (Eqs 33–37), although difficulties are sometimes encountered. Low yields of α′-alkylation products were frequently obtained from the methylthiomethylene and α-oxo ketene dithioacetal derivatives of cyclopentanones.[46a,74b] Cyclic vinylogous thiol esters undergo[75] α′-alkylation with LDA (Eq. 34) and α-alkylation with KH (Eq. 35),

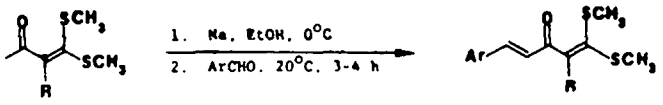


eq. 33



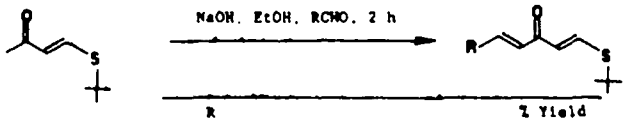
eq. 34

eq. 35



R	Ar	% Yield
Me	Ph	90
Me	p-$MeOC_6H_4$	90
Et	Ph	90
n-Pr	Ph	48
i-Pr	Ph	71
n-Bu	Ph	65

eq. 36

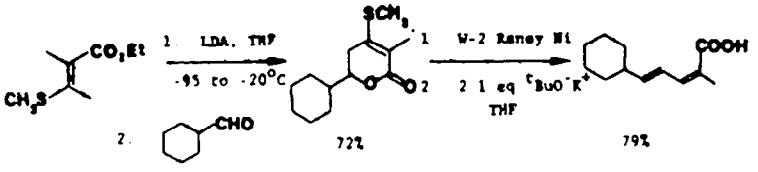


R	% Yield
Ph	81
PhCH=CH	84
p-$MeOC_6H_4$	82
p-$MeOC_6H_4(CH=CH)_2$	61
p-HOC_6H_4	47

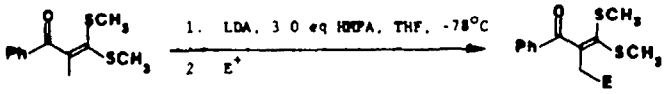
eq. 37

although the latter[75c] procedure could not be effectively controlled for monoalkylation. This is in contrast to β-amino-α,β-enones and enoates which generally undergo γ-alkylation.[75c,76] Deprotonation and γ-alkylation of β-alkylthio-α,β-enoates have been exploited, however, in the synthesis of α,β-γ,δ-dienoic acids (Eq. 38).[77]

Deprotonation studies involving α-oxo ketene dithioacetals with no α'-H have been reported.[78] Allyl and vinyl carbanions can be generated from β,β-bis(alkylthio)-α,β-enones containing an α-Me or H, respectively, and quenched with a variety of electrophiles (Eqs 39 and 40). When a substituent other than methyl or hydrogen is present at the α-position, deprotonation occurs adjacent to the S heteroatom and subsequent intramolecular cyclization to a thiophene occurs (Eq. 99, Table 21). α,β-Bis(alkylthio)-α,β-enones containing no alkyl group at the α-C atom undergo deprotonation at both the vinyl carbon and adjacent to the S heteroatom (Eq. 40) and the ratio is base dependent. Deprotonation adjacent to sulfur does not occur for the ethylthio analogs.

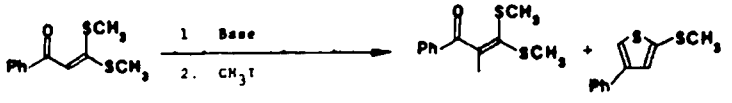


eq. 38



E	% Yield
DCl	90
MeI	70
PhCHO	65
$PhCOCH_3$	25
$CH_3COCH=CMe_2$	40
EtO_2CCH_2Br	35
$PhCO_2CH_3$	42
MeSSMe	50

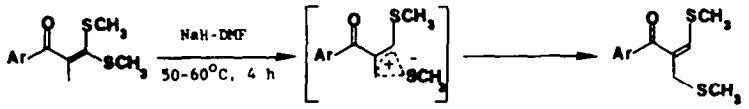
eq. 39



LDA	35%	30%
LHMDS	90%	—

eq. 40

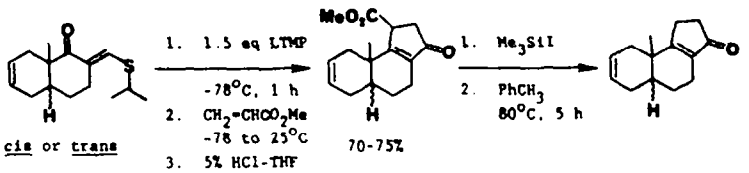
Junjappa and co-workers[79] have reported a base-catalyzed rearrangement of α-methyl-β,β-bis(alkylthio)-α,β-enones to α-alkylthiomethyl-β-alkylthio-α,β-enones (Eq. 41). The rearrangement proceeds in low to moderate yields with NaH/DMF and the yields are sensitive to reaction times. Utilization of sodium ethoxide in ethanol at room temperature affords starting material while heating the solution to reflux affords polymeric material. The reaction involves initial deprotonation to afford an allylic carbanion which is believed to rearrange via a concerted sulfur assisted polar mechanism similar to that proposed for other thioallylic rearrangements.



eq. 41

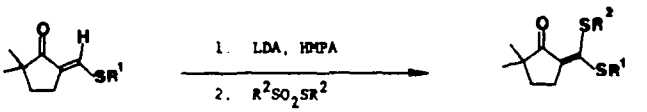
R (p-R-Ar)	% Yield
H	35
MeO	45
Me	35

Vinylogous thiol esters containing no α'-H or β-alkyl substituents undergo deprotonation to afford vinyl carbanions and not allylic carbanions as originally reported.[80] These vinyl anions have been employed in an elegant cyclopentanone annulation sequence (Eq. 42).[80a] α-Oxo ketene dithioacetals containing two different alkylthio substituents have been prepared by sulfenylation of these vinyl anions (Eq. 43).[46a] Similar vinyl carbanions have been generated from β-arylthio-α,β-unsaturated esters[81] and acids[81b] (Eqs 44 and 45). These vinyl carbanions were alkylated with α,β-enoates, acid



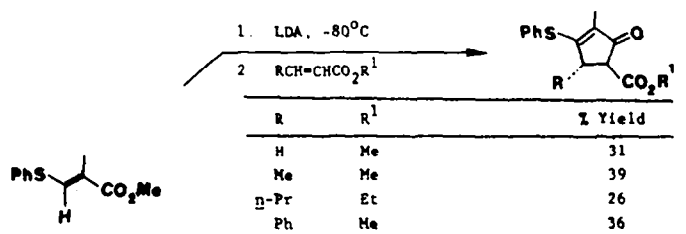
cis or trans

eq. 42



eq. 43

R^1	R^2	% Yield
Et	Me	76
Me	Et	73



eq. 44

R	R^1	% Yield
H	Me	31
Me	Me	39
n-Pr	Et	26
Ph	Me	36

eq. 45

R	% Yield
Et	20
i-Pr	47
t-Bu	72
Ph	32

chlorides, and aldehydes to afford cyclopentenones, γ-keto-α,β-enoates, and butenolides (*vide infra*), respectively. Alkyl halides appear not to have been examined and may not be sufficiently electrophilic for these vinyl carbanions. The vinyl carbanions derived from the esters did not react with ketones and the carbanion could not be cleanly generated from methyl 3-phenylthio-2-propenoate. These problems were surmounted by utilization of the dianions derived from the carboxylic acid derivatives.

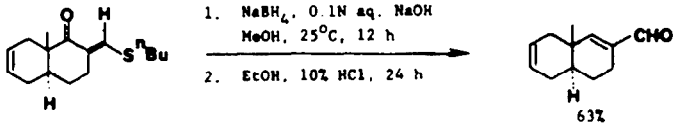
Clearly, alkylation of carbanions derived from β-alkylthio- and β,β-bis(alkylthio)-α,β-enones and enoates provides an opportunity to elaborate the carbon skeleton prior to manipulation of the functionality in subsequent transformations.

3. REDUCTION REACTIONS AND CHEMISTRY INVOLVING 1,2-NUCLEOPHILIC ADDITION

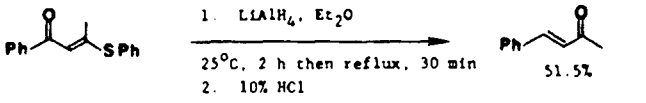
3.1. *Reduction reactions and the* 1,3-*carbonyl transposition*

The reduction of α,β-unsaturated carbonyl compounds containing either one or two β-alkylthio (or arylthio) substituents can follow several pathways depending upon the substrate and reducing reagent. Simple reduction of the ketone carbonyl affords an allylic alcohol which can undergo an acid-promoted aniontropic rearrangement[82] to afford a new transposed α,β-unsaturated carbonyl compound. Alternatively, reduction can also be effected at the C=C, the C—S bond, or at both the carbonyl and olefin functionalities. The development of procedures for effectively controlling these reduction pathways, as well as the allylic rearrangement, has enhanced considerably the synthetic utility of vinylogous thiol esters and α-oxo ketene dithioacetals.

Ireland and Marshall developed the n-butylthiomethylene functionality as a blocking group for a methylene position adjacent to a ketone and exploited the functionality in several ways that utilized reduction procedures. A 1,3-carbonyl transposition methodology[3b,44,83] modeled on procedures developed for alkoxymethylene derivatives[84] involved reduction of the ketone carbonyl with sodium borohydride followed by an acid-promoted rearrangement of the intermediate allylic alcohol (Eq. 46). This 1,3-carbonyl transposition methodology provides for ketone–aldehyde (Eq. 46) and ketone–ketone (Eq. 47) interconversions. The synthesis of β-alkyl-β-alkylthio-α,β-enones from α-oxo ketene dithioacetals[46] or acetylenic ketones[46a,68a] provides considerable versatility. Since the pioneering efforts of Ireland and Marshall this strategy has been examined by several workers for β-alkylthio-α,β-enones[44,68,85] and has only recently been achieved in synthetically useful yields with α-oxo ketene dithioacetals.[44,86,87]

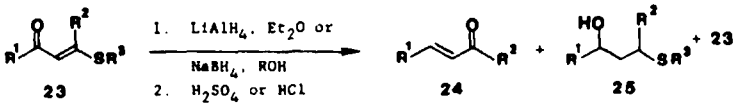


eq. 46



eq. 47

The reduction of vinylogous thiol esters with $LiAlH_4$ or $NaBH_4$ was extensively investigated by Nishio and Omote.[85] The chemoselectivity and efficiency of the reductions was dependent upon the substrate structure (**23**), reducing reagent, and reaction conditions (Eq. 48, Table 9). Generally, reduction with either $LiAlH_4$ or $NaBH_4$ effected 1,2-reduction of the ketone carbonyl to afford an intermediate allylic alcohol which rearranged to the transposed carbonyl compound (**24**) upon work-up with aqueous mineral acids. In certain instances, however, the γ-hydroxy sulfide (**25**) was produced in an over-reduction process. It is clear that the over-reduction occurs to a significantly greater extent with $LiAlH_4$ than with $NaBH_4$ and with substrates containing either a β-H or β-phenyl substituent.



eq. 48

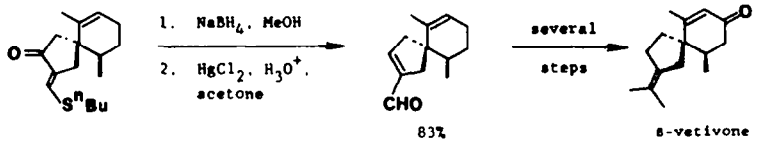
Table 9. Reduction of vinylogous thiol esters with $NaBH_4$ and $LiAlH_4$

Substrate 23			Reagent	Rxn	Products			Ref
R^1	R^2	R^3	(equivs)	Cond[a,b]	24	25	23	
Ph	Me	Et	$LiAlH_4$(1)	A	91			85a
			(1)	B	24-28		40-60	85a
			$NaBH_4$ (1)	C	46-49		30-33	85a
Ph	Ph	Et	$LiAlH_4$(2)	D	trace	91.5	trace	85a
			$NaBH_4$ (2)	C	37.5	14.5	36.0	85b
Ph	H	Ph	$LiAlH_4$(2)	D	4.0	85.5		85b
			$NaBH_4$ (2)	C	49		20	85b
PhCH=CH	H	t-Bu	$LiAlH_4$(1)	E	69			68a
Me	Ph	Et	$LiAlH_4$(2)	D		100		85b
			$NaBH_4$ (1)	C	18.5		69.5	85b
Me	Me	Ph	$LiAlH_4$(2)	D	62.5		7.0	85b
			$NaBH_4$ (2)	C	22.0		5.5	85b
$-(CH_2)_3-$		Et	$LiAlH_4$(2)	D	35.5			85b
			$NaBH_4$ (1)	C	24.0			85b

[a] A = Et_2O, reflux 1 h. B = Et_2O, rt, 25 h. C = MeOH or EtOH, rt, 2 h. D = Et_2O, 2 h, rt, reflux 0.5 h. E = Et_2O, -15°C, 3 h. [b] Reactions were worked-up or treated with either aqueous HCl or H_2SO_4 resulting in rearrangement and hydrolysis of the initially formed γ-hydroxy vinyl sulfides.

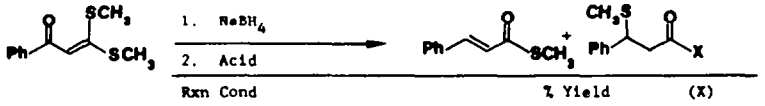
Although the authors suggest that the over-reduction product arises via initial 1,4-reduction of the enone,[85b] it appears more likely that an initially formed allylic alcohol undergoes subsequent reduction to afford the γ-hydroxy sulfide (Eq. 55 and structure 32). From this perspective, the selective over-reduction of substrates containing either a β-H or β-phenyl substituent can be understood in terms of steric and electronic factors, respectively.

Nishio and Omote reported relatively low yields for the $NaBH_4$ reduction of both aliphatic ketones and the less electrophilic aryl ketones and although the yields could be improved by the addition of $CeCl_3 \cdot 7H_2O$[85b] they are still low (50.5–76%) in contrast to the relatively high yields reported in several synthetic applications.[88] In the synthesis of β-vetivone, this 1,3-carbonyl transposition methodology was exploited to control the orientation of the isopropylidene group (Eq. 49).[88a]



eq. 49

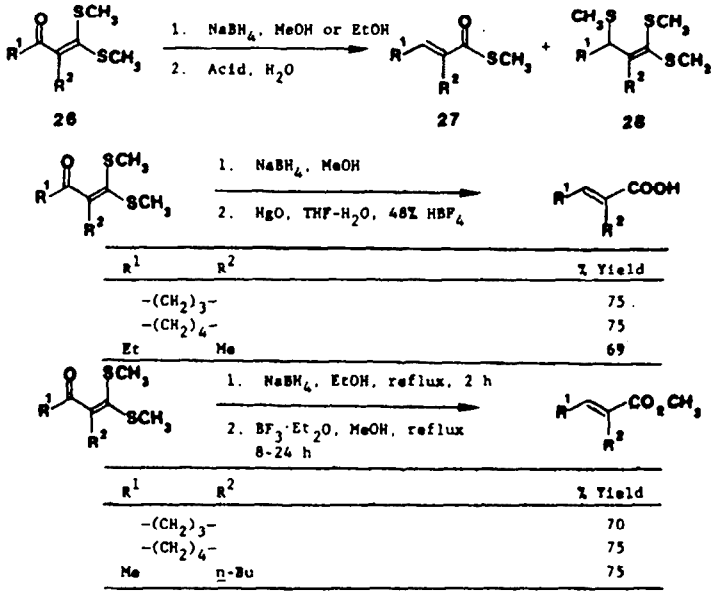
In principle, utilization of α-oxo ketene dithioacetals in a similar 1,3-carbonyl transposition process would provide a procedure for effecting a ketone–ester interconversion. Although the 1,2-reduction of α-oxo ketene dithioacetals with $NaBH_4$ was reported as early as 1969 by Saquet and Thuillier[89] to occur in high yields, treatment of the intermediate allylic alcohols with *p*-toluenesulfonic acid in refluxing benzene afforded low yields of the expected S-methyl α,β-unsaturated thiol esters in addition to other products (Eq. 50). The formation of β-methylthio thiol esters was suggested to occur by conjugate addition of methanethiol to the initially formed α,β-unsaturated thiol ester. Reinvestigation[87] confirmed the formation of β-methylthio thiol esters as the principal product when



Rxn Cond	% Yield		(X)
p-TsOH, PhH, reflux	44	44	(SMe)
10% aq. HCl, MeOH, 25°C		45	(SMe)
80% aq. CF_3COOH, reflux		65	(SMe)
conc. H_2SO_4, MeOH, reflux		43	(OMe)
$BF_3 \cdot Et_2O$, H_2O, reflux	55		

eq. 50

either HCl or CF_3COOH was employed (Eq. 50). Dieter and co-workers discovered[44,86] that although mineral acids such as HCl and H_2SO_4 afforded low yields of the α,β-unsaturated thiol esters, utilization of 10% (v/v) aqueous HBF_4 in THF (1 : 4) afforded in high yield a nearly 1 : 1 mixture of the desired thiol ester (27) and a methyl sulfide by-product (28) presumably arising from methanethiol trapping of a very stable secondary allylic carbocation (Eq. 51). Utilization of sulfur complexing agents [e.g. HgO, $Hg(OAc)_2$] provided a solution to this problem, although the yield of thiol ester was crucially dependent upon the quantity of HgO employed. Addition of 0.75 equivalents of HgO cleanly afforded the S-methyl α,β-unsaturated thiol esters (Eq. 51 and Table 10) while addition of two or more equivalents of HgO cleanly afforded the α,β-unsaturated acids in good yields (Eq. 52). Subsequently, Junjappa and co-workers[87] reported that treatment of the intermediate α-hydroxyketene dithioacetals with $BF_3 \cdot Et_2O$ in H_2O heated at reflux afforded good yields of thiol esters (Table 10) while treatment with $BF_3 \cdot Et_2O$ in methanol afforded good yields of α,β-unsaturated methyl esters (Eq. 53). The latter

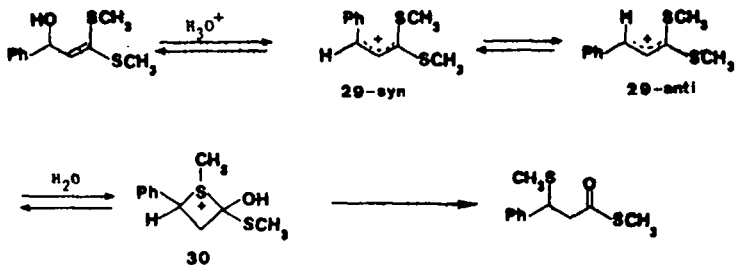


procedure has been utilized in the synthesis of methyl 7-aryl-2,4,6-heptatrienoates. In this synthetic sequence, the 1,3-carbonyl transposition methodology was applied to α-oxo ketene dithioacetals prepared by the aldol condensation of 4,4-bis(methylthio)-3-buten-2-one or 3-methyl-4,4-bis(methylthio)-3-buten-2-one with cinnamaldehydes (see e.g. Eq. 36).[74a] Consequently, $NaBH_4$

Table 10. Reduction of α-oxo ketene dithioacetals with $NaBH_4$ and rearrangement of the intermediate allylic alcohols

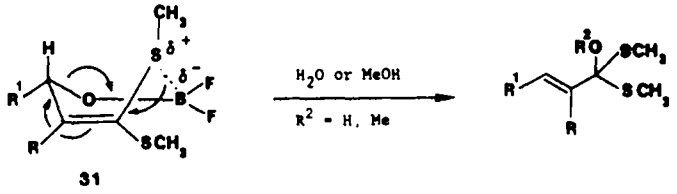
Substrate 26 R^1	R^2	Allylic Alcohol % Yield[a]	Rxn Cond[b]	Products 27	28	Ref
$-(CH_2)_3-$		98	A	50	47	44, 86
			B	75		44, 86
			C	55		87
$-CHCH_3CH_2CH_2-$		98	A	44	35	44, 86
			B	50		44, 86
$-(CH_2)_4-$		96	A	58	24	44, 86
			C	70		87
Et	Me	96	B	79		44, 86
Ph	H		C	55		87
p-MeC_6H_4	H		C	75		87

[a]Yields are based upon crude products which were greater than 95% pure by NMR.
[b]A = 10% HBF_4, THF, rt. B = 10% HBF_4, THF, 0.50-0.70 equiv of HgO, rt.
C = i. $BF_3 \cdot Et_2O$, Et_2O, 5 min. ii. H_2O, reflux, 12-16 h.



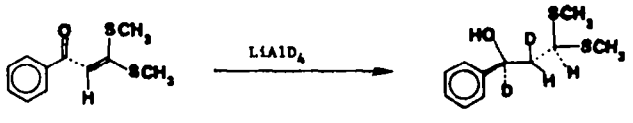
Scheme 2.

reduction of α-oxo ketene dithioacetals affords excellent yields of α-hydroxyketene dithioacetals which can be converted into α,β-unsaturated acids, methyl esters, or thiol esters depending upon the particular reaction conditions employed. The allylic rearrangement appears to occur in high yield only when HBF_4 or $BF_3 \cdot Et_2O$ are employed as the acid and the clean formation of thiol esters requires the use of HgO or higher reaction temperatures. The failure of mineral acids to cleanly effect the aniontropic rearrangement may be a result of inter- or intramolecular attack of sulfur at the carbocation center. It has been pointed out, that the β-methylthio thiol esters may arise via conjugate addition of methanethiol to the α,β-unsaturated thiol esters or via an intramolecular process (Scheme 2) involving a thiatanium ion **30**. Junjappa has suggested that the effectiveness of HBF_4 may result from complexation of the B atom to oxygen and sulfur to form a 6-membered transition state **31** which would effectively diminish the intramolecular participation of the S atom. The secondary allylic alcohols rearrange to form the *E* stereoisomers exclusively and this stereoselectivity can be understood either in terms of a boat-like transition state or in terms of a free carbocation. In Junjappa's proposed boat-like transition state the larger substituent at C1 will prefer the less sterically crowded *exo* position leading to the *E* stereoisomer (Eq. 54). Alternatively, the more stable free carbocation would have the larger substituent at C1 *anti* (**29**-*anti*) to the methylthio substituent at C3 and would also lead to the *E* stereoisomer (Scheme 2) (*vide infra*).[90]



eq. 54

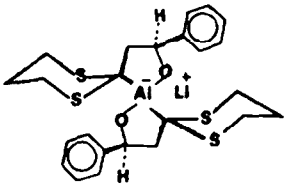
Gammill *et al.*[91] have examined the $LiAlH_4$ reduction of α-oxo ketene dithioacetals. They discovered that both the carbonyl and olefin functionalities are reduced to afford γ-hydroxy dithioacetals. The reaction was shown to proceed in a stereospecific fashion by utilization of $LiAlD_4$ and to occur with quantitative conversion with 0.5 equivalents of reagent (Eq. 55). The stereospecificity of the reaction and the characterization of an intermediate organoaluminum species (**32**) confirm that the reduction process proceeded by an initial regiospecific reduction of the ketone carbonyl followed by an intramolecular hydroalumination of the double bond. Additional support derives from a reported reduction of an α-hydroxy ketene dithioacetal in which the double bond was similarly reduced.[92] The reaction is, however, sensitive to steric constraints which interfere with the hydroalumination step. Under these conditions, an alternative reaction pathway involving a reduction–alkylation–



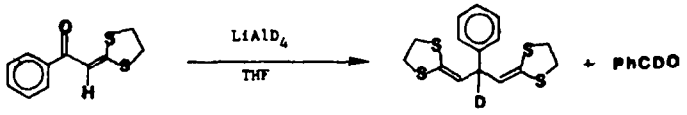
eq. 55

fragmentation mechanism is available (Eq. 56). In a subsequent work,[93] Gammill established that this reduction process could be exploited to afford diastereomerically pure *threo* β-alkyl γ-bis(methylthio) alcohols in excellent yield (Table 11). The reaction is formally equivalent to an aldol addition reaction and provides a new strategy for acyclic diastereoselection. The reaction shows diminished yields for C2 alkyl substituents other than methyl and in one instance the reduction stopped at the allylic alcohol stage as a result of steric interactions. The reduction can also be controlled to afford only the allylic alcohol by employing lower reaction temperatures.

Reduction of α-oxo ketene dithioacetals with the electrophilic reducing reagents DIBAL, 9-BBN, and catecholborane was also examined.[94] DIBAL and catecholborane gave predominantly the 1,4-

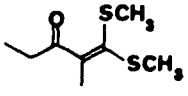
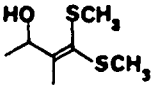
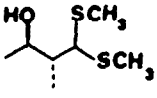
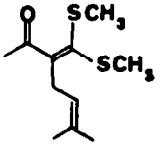
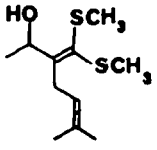
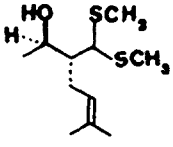
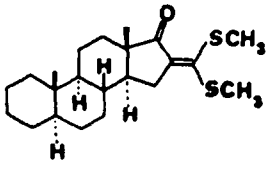
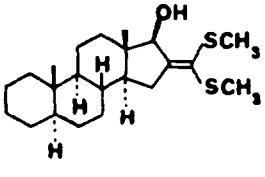


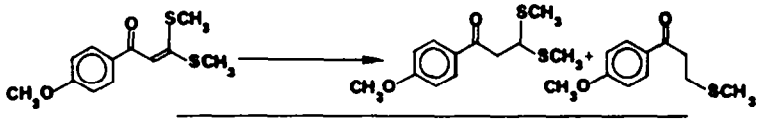
32



eq. 56

Table 11. Reduction of α-oxo ketene dithioacetals with $LiAlH_4$[93]

Substrate	Rxn Cond	% Yield	Product
	25°C, THF	95	
	reflux, THF	98	
	-25°C, THF	91	
	50°C, 3 h, THF	71	
	reflux, THF	87	



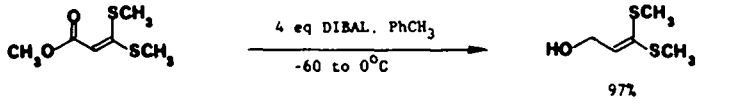
Rxn Cond	% Yield		
DIBAL-Et_3N, THF, -78°C	83	—	
Catecholborane, THF, 0°C	56	10	
9-BBN, THF, 25°C		53	

eq. 57

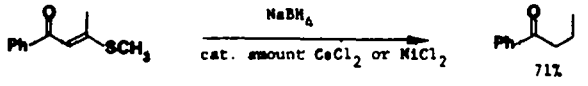
reduction product while 9-BBN effected over-reduction to the ketosulfide (Eq. 57). In the DIBAL reductions, triethylamine was added to suppress the 1,2-reduction process. Reduction of a β,β-alkylthio-α,β-enoate with DIBAL in an attempt to prepare an α-formyl ketene dithioacetal afforded a 1 : 1 mixture of the starting ester and the allylic alcohol. The allylic alcohol could be prepared in good yield by utilization of excess DIBAL (Eq. 58).[31] α-Hydroxy ketene dithioacetals have also been prepared by $NaBH_4$ reduction of α-formyl ketene dithioacetals,[40] and by $LiAlH_4$ reduction of β,β-bis(alkylthio)-α,β-enoates.[89]

Nisho and Omote[85b] effected similar reductions of vinylogous thiol esters employing $NaBH_4$ in the presence of metal hydrides. Although utilization of $NaBH_4$–$CeCl_3 \cdot 7H_2O$ resulted only in higher yields of allylic alcohols via 1,2-reduction of the carbonyl, $NaBH_4$ in the presence of a catalytic amount of cobalt(III) chloride or nickel chloride reduced both the olefin and the C—S bond (Eq. 59) to afford saturated ketones. Similar reductions could not be effected with $NaBH_4$–$FeCl_2$, $NaBH_4$–$FeCl_3$, $NaBH_4$–CuI, $NaBH_4$–$CuCl_2$, or $LiAlH_4$–$CoCl_2$ and 1-phenyl-3-ethylthio-1-butanone was recovered unchanged upon treatment with $NaBH_4$–$CoCl_2$ suggesting that reduction of the C—S bond occurs prior to reduction of the olefin. Interestingly, Junjappa and co-workers[65] have reported the chemoselective reduction of α-oxo ketene dithioacetals with $NaBH_4$–$NiCl_2$ to afford vinylogous thiol esters in yields of 42–77% (Eq. 60). One major stereoisomer was generally formed predominantly and the formation of either the *E* or *Z* stereoisomer varied in a manner suggesting the influence of both steric and electronic factors.

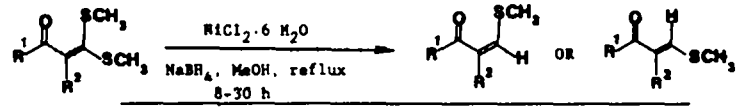
Ireland and Marshall[3a] also exploited the n-butylthiomethylene group for the regiospecific introduction of a methyl substituent by reductive desulfurization with W-2 Raney Ni or with sodium in liquid ammonia. The latter conditions were required for substrates containing non-conjugated double bonds. Buchi *et al.* employed this strategy[95] in their synthesis of loganin (Eq. 61). Coates and Sowerby extended the metal–ammonia reduction procedure by trapping the resulting enolate anion with



eq. 58

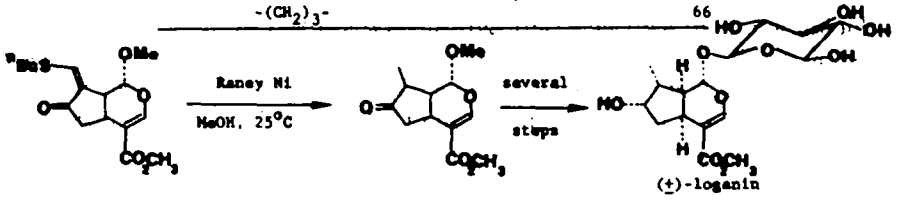


eq. 59

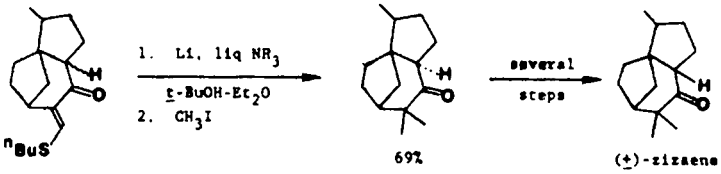


R^1	R^2	% Yield	
Ph	H		62
p-MeC_6H_4	H	64	
p-ClC_6H_4	H		50
Ph	Et	57	
p-MeC_6H_4	Me	56	
Me	H		77
-$(CH_2)_3$-			66

eq. 60



eq. 61

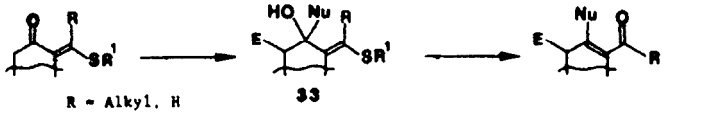


eq. 62

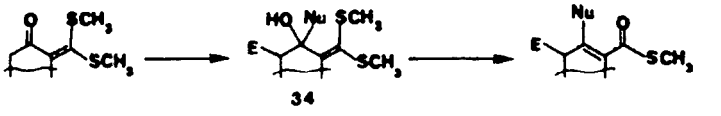
electrophiles to afford site-selective geminal alkylation[96a] and employed this strategy in a synthesis of (±)-zizaene (Eq. 62).[96b]

3.2. *The alkylative 1,3-carbonyl transposition methodology*

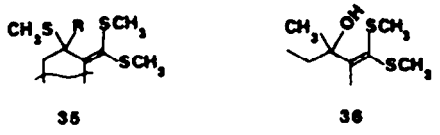
The addition of Grignard and organolithium reagents to the ketone carbonyl of vinylogous thiol esters or α-oxo ketene dithioacetals provides considerable potential for the sequential regioselective construction of new C—C bonds. Formation of C—C bonds occurs during the alkylative carbonyl transposition sequence while alkylation of the original or transposed carbonyl compound, or both, provides for additional bond forming opportunities (Eqs 63 and 64). While the vinylogous thiol esters afford an unsaturated aldehyde or ketone, the α-oxo ketene dithioacetals yield an unsaturated thiol ester. This transformation provides for additional synthetic flexibility revolving around the thiol ester functionality.



eq. 63

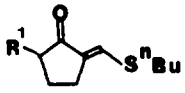
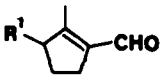
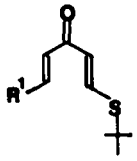
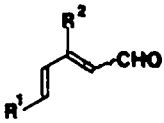
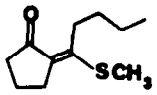
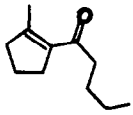
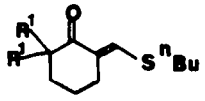
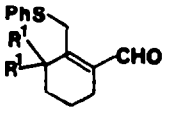


eq. 64

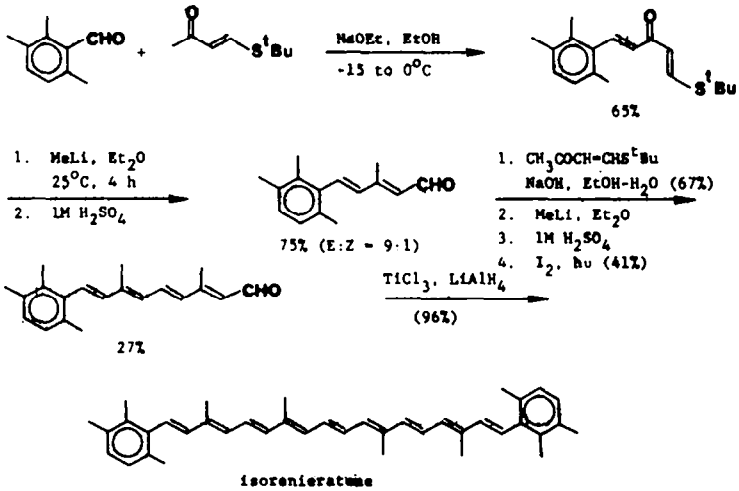


The reaction of organolithium reagents with vinylogous thiol esters[46b,68,97] generally proceeds in high yield to afford the transposed carbonyl compounds upon acid-promoted rearrangement of the intermediate γ-hydroxy vinyl sulfides **33** (Eq. 63, Table 12). It is interesting to note that the aniontropic rearrangement proceeds in good yield with sulfuric acid. Nakagawa and co-workers examined this methodology for the synthesis of enals and dienals.[68] The latter compounds were readily obtained by effecting the alkylative carbonyl transposition on dienones prepared by the aldol condensation of 4-(t-butylthio)-3-buten-2-one with various aldehydes (Eq. 37). The acyclic substrates afforded a mixture of *E* and *Z* stereoisomers, although the *E* stereoisomers were generally formed as the major product and the stereoselectivity varied widely with no apparent pattern. A single stereoisomer was observed, however, in the reaction of 1-lithioalkynes with vinylogous thiol esters and was shown to have the *E* configuration (Table 12). Combination of the aldol condensation reaction with the 1,3-carbonyl transposition sequence provides for a reiterative process which Nakagawa and co-workers exploited in a synthesis of isorenieratene (Scheme 3).[68b] Since the configuration of the double bond in the vinylogous thiol esters is not important in these applications, the vinylogous thiol esters can be prepared by the addition of thiolate anions to acetylenic ketones or stereoselectively by the reaction of organocuprates with α-oxo ketene dithioacetals (Eq. 81).[46] The 1,2-nucleophilic addition of ester enolate anions to vinylogous thiol esters followed by acid-promoted aniontropic rearrangement has recently been exploited in a synthesis of α-pyrones (Schemes 10 and 11, Table 28).[98,99] The 1,2-nucleophilic addition of [(phenylthio)methyl]lithium to vinylogous thiol esters has been utilized in a reductive alkylation procedure[100a] and in a synthesis of furans and butenolides (Eq. 121).[100b]

Table 12. Addition of organolithium reagents to vinylogous thiol esters in an alkylative 1,3-carbonyl transposition methodology

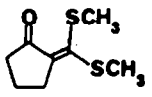
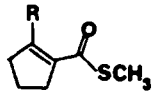
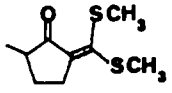
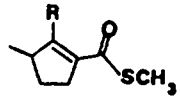
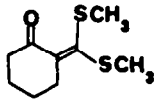
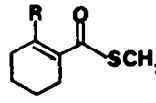
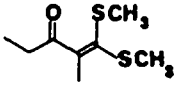
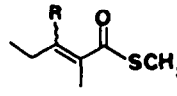
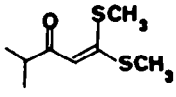
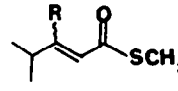
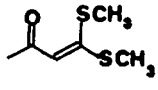
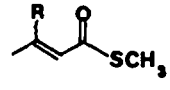
Substrate	R^1	Nucleophile R^2-Metal	% Yield	(E : Z)	Product	Ref
	methallyl	CH_3Li	55			97
	allyl		61			97
	n-Pr		66			97
	Ph	CH_3Li	68	45:55		68a
		HC≡CLi	98	100:0		68a
	p-$MeOC_6H_5$	CH_3Li	81	80:20		68a
		n-Bu	83	50:50		68a
		HC≡CLi	90	100:0		68a
	2,4,6-$Me_3C_6H_2$	CH_3Li	75	90:10		68a
		CH_3Li	60			46b
	H	$PhSCH_2Li$	82			100a
	CH_3		90			100b

Dieter and co-workers[44,86] examined an alkylative 1,3-carbonyl transposition methodology involving α-oxo ketene dithioacetals (Table 13). The 1,2-nucleophilic addition of Grignard and alkyl, alkenyl, and alkynyl organolithium reagents occurred in excellent yield to afford tertiary allylic alcohols (34, Eq. 64). Again, treatment of these α-hydroxy ketene dithioacetals (34) with mineral acids afforded poor yields of the α,β-unsaturated thiol esters. These products could only be obtained in high yield by treatment of the alcohols with HBF_4 in aqueous THF. The tertiary allylic alcohols did not require the addition of HgO as the methylsulfide by-products (35) were formed in less than 2%.



Scheme 3.

Table 13. Addition of organolithium reagents to α-oxo ketene dithioacetals in an alkylative 1,3-carbonyl transposition methodology[44]

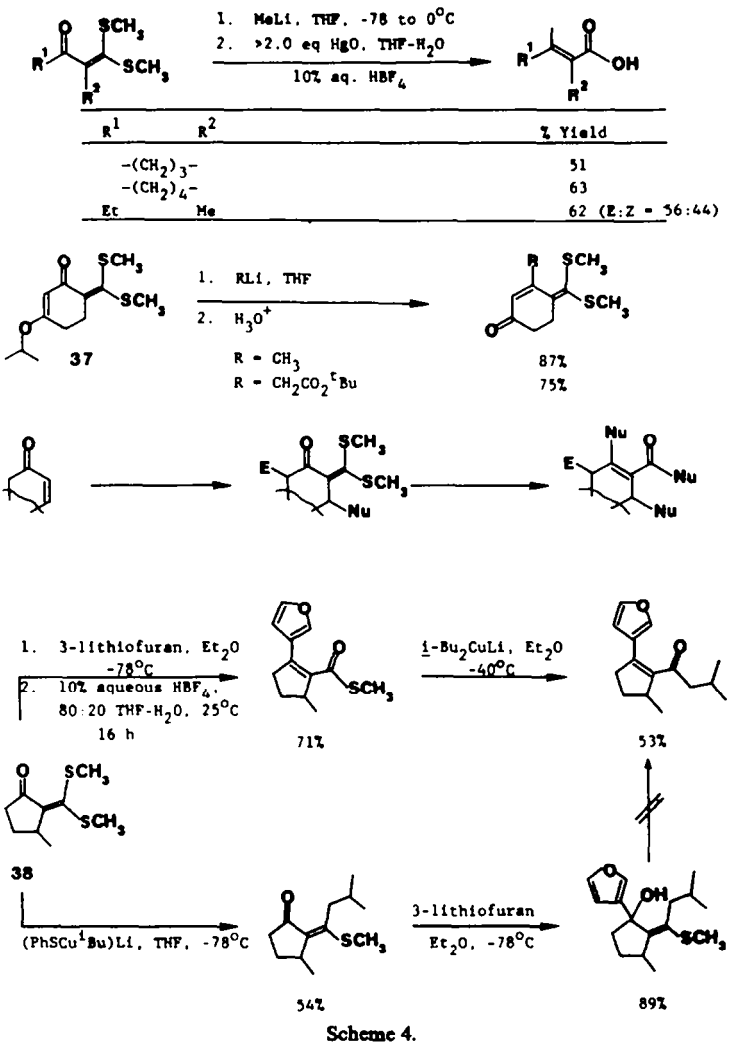
Substrate	Nucleophile R-Metal	Alcohol % Yield[a,b]	Product[a]	% Yield (E : Z)[c]
	CH_3Li	69		78
	HC≡CHLi	80		40
	$Me_3SiCH{=}CHCH_2Li$	89		66
	CH_3Li	80		52[d]
	CH_3Li	82		72
	$Me_3SiCH{=}CHCH_2Li$	88		78
	CH_3Li	76		68 (78:22)
	$Me_3SiCH{=}CHCH_2Li$	92		40 (42:58)
	CH_3Li			73 (80:20)
	$Me_3SiCH{=}CHCH_2Li$			56 (60:40)
	$(CH_3)_3CLi$			58 (85:15)
	$CH_3(CH_2)_2C{\equiv}CLi$			52 (5:95)

[a]Yields are based upon isolated products purified by chromatography on silica gel. [b]The allylic alcohols were converted into the α,β-unsaturated thiol esters by the action of 10% aq. HBF_4 in $THF:H_2O$ (4:1) at room temperature. [c]Assignments were made by NMR chemical shifts. [d]This reaction also afforded the methyl sulfide by-product (e.g. 35) in 10% yield.

Utilization of two equivalents of HgO, however, cleanly afforded the unsaturated acids (Eq. 65). The acyclic substrates afforded a mixture of *E* and *Z* stereoisomers in which the *E* isomer generally predominated. Poor stereoselectivity was obtained when allyltrimethylsilyl carbanion was employed as the nucleophile; the stereoisomer having the allyl substituent *syn* to the thiol ester carbonyl predominated. Although α-hydroxy ketene dithioacetal **36** afforded mainly the *E* (78:22) thiol ester and the *E* (56:44) carboxylic acid upon controlled hydrolysis, the latter process exhibited very little stereoselectivity. The favored formation of the *E* stereoisomer parallels the results of Nakagawa and co-workers[68a] and Trost and Stanton[90] for the hydrolysis of γ-hydroxy vinyl sulfides. The suggestion of Trost and Stanton that the isomer distribution can be understood in terms of intermediate carbocation stabilities would account for the modest stereoselectivity favoring the isomer having the larger substituent *trans* to the carbonyl (Scheme 2). The stereoselectivities could also be understood in terms of a cyclic 6-membered transition state involving complexation of boron to the O and S atoms of the α-hydroxy ketene dithioacetal (Eq. 54).

The α-oxo ketene dithioacetal **37** also contains a vinylogous ester moiety which may participate in a 1,3-carbonyl transposition process. Addition of methyllithium or lithium t-butyl acetate to **37** followed by quenching with 10% HCl afforded enones in which the ketene dithioacetal functionality remained intact (Eq. 66).

The successful preparation of regiospecifically substituted α-oxo ketene dithioacetals (Eq. 9) and the known acylation of organocuprates by thiol esters[101] enhances considerably the synthetic potential of the alkylative carbonyl transposition methodology for the sequential regioselective construction of new C—C bonds (Eq. 67). Dieter and Dieter have exploited[43] this strategy in a short and efficient



Scheme 4.

synthesis of the toxic furanosesquiterpene (±)-myodesmone (Scheme 4). An alternative route[44] utilized a vinylogous thiol ester prepared by reaction of the regiospecifically substituted α-oxo ketene dithioacetal (**38**) with lithium diisobutylcuprate (*vide infra*). Although the addition of 3-lithiofuran to the vinylogous thiol ester proceeded in high yield, the resulting allylic alcohol could not be induced to undergo rearrangement to myodesmone. Although the two different sequences of operations are formally equivalent they are not equally successful in this specific synthesis.

3.3. *Cyclization reactions*

Interestingly, 1,2-nucleophilic addition of allyltrimethylsilyl carbanion to α-oxo ketene dithioacetals afforded the transposed α,β-unsaturated thiol esters in good yields (Table 13) while addition of methylallyl magnesium chloride afforded cyclization products (Table 14).[44] The α,β-unsaturated thiol esters derived from α-oxo ketene dithioacetals and allyltrimethylsilyl carbanion contain a vinyl silane moiety which can in principle undergo intramolecular acylation to afford a phenol. This intramolecular acylation of the vinyl silane derivative proved unsuccessful with a wide range of Brönsted and Lewis acids. Eventually, dimethyl methylthiosulfonium fluoroborate was found to effect cyclization of thiol ester **39** (Eq. 68) to the annulated phenol in good yield. The 5-membered ring

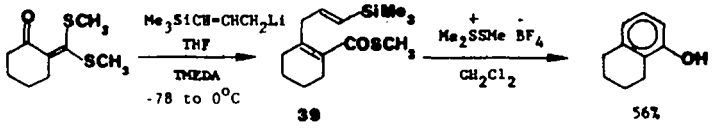
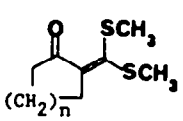
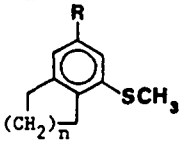
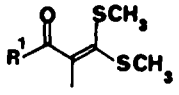
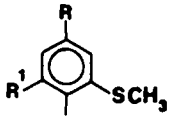
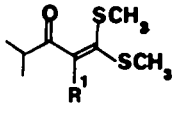
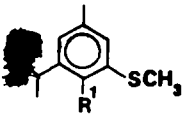
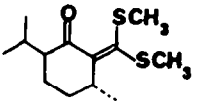
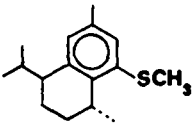
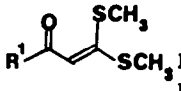
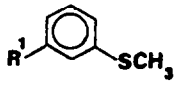
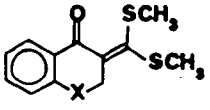
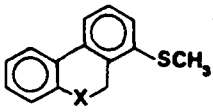


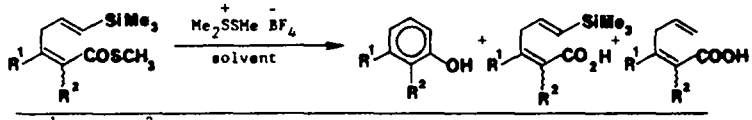
Table 14. Synthesis of aryl methylthio esters from α-oxo ketene dithioacetals

Substrate	R^1, n or X	Grignard[a] R	Alcohol % Yield	Rxn Cond[b]	% Yield	Product	Ref
	1	Me	85	A	62		103
		H		B	64		104
	2	Me	92	A	64		103
				C	87		103
		H		B	74		104
	Et	Me	60	A	47		103
				D	52		103
		H		B	40		104
	H	Me		D	43		103
	Me	Me	80	E	47		103
		Me	89	D	88		103
	Ph	H		B	45		104
	p-$MeOC_6H_4$	H		B	39		104
	p-ClC_6H_4	H		B	40		104
	S	H		B	67		104
	O	H		B	64		104

[a] R = Me for methallylmagnesium chloride. R = H for allylmagnesium bromide.
[b] A = $HgCl_2$, CH_3CN, 60-70°C, 1 h. B = $BF_3 \cdot Et_2O$, PhH, reflux, 30 min. C = 10% (v/v) HBF_4 (1 part), THF:H_2O (4:1). D = $BF_3 \cdot Et_2O$, CH_3NO_2, 1 h. E = $AlCl_3$, CH_3NO_2, 0°C.

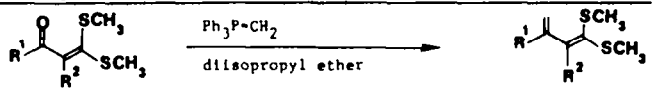
and acyclic substrates, however, afforded moderate to poor yields of phenols and gave rise to side products arising from ester hydrolysis and ester hydrolysis and desilylation of the vinyl silane (Eq. 69). The low yields of cyclization products may reflect the presence of the large trimethylsilyl group at the terminal position of the participating olefin. An unsuccessful attempt to circumvent this problem was made by treating the α-oxo ketene dithioacetals with the allyltrimethylsilyl Grignard reagent. γ-Alkylation occurred to afford α-hydroxy ketene dithioacetals containing an allyl silane moiety. These allylic alcohols, however, proved resistant to hydrolysis and the unsaturated thiol esters could not be obtained.[102]

The 1,2-nucleophilic addition of methylallyl magnesium chloride[44,103] and allyl magnesium bromide[104] to α-oxo ketene dithioacetals followed by treatment with Brönsted or Lewis acids afforded aryl methylthio ethers (Table 14) instead of the thiol ester transposition product. This procedure provided good to excellent yields of annulated aromatic compounds and modest yields of simple substituted benzene derivatives. The methylthio substituent can be exploited as a protecting and directing group or as a leaving group in a substitution reaction with primary alkyl Grignard reagents in the presence of Ni catalysts.[103] This direct substitution reaction provides an attractive alternative route to substituted benzenes which otherwise could be prepared in low yields from the corresponding vinylogous thiol esters.[103] This methodology was exploited in a short synthesis of *trans*-calamenene. The fact that the product was contaminated with the *cis*-diastereomer indicated that isomerization had occurred to the extent of 16% during the acid-promoted cyclization process.[103] The generality of this



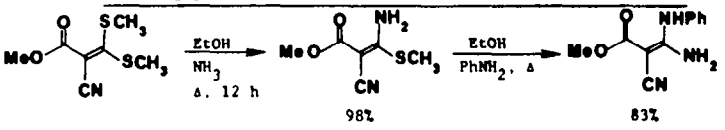
eq. 69

R^1	R^2	Solvent	% Yield		
Et	Me	CH_3CN	37	27	28
i-Pr	H	CH_2Cl_2	30		
$-(CH_2)_3-$		CH_2Cl_2	17		11



eq. 70

R^1	R^2	% Yield
H	Me	80
Me	Me	84
H	Ph	61
$-(CH_2)_3-$		85
$-(CH_2)_3-$		90



eq. 71

methodology appears to be limited, presumably because of the steric interactions present at the positions of ring closure.

3.4. *Miscellaneous reactions*

Several other nucleophiles have been added to vinylogous thiol esters and α-oxo ketene dithioacetals in a 1,2-fashion. Reaction of these substrates with Wittig reagents affords 1-alkylthio-[105] and 1,1-bis(alkylthio)-1,3-dienes (Eq. 70).[106a] Although the use of carbonyl stabilized Wittig reagents were not reported, δ,δ-bis(methylthio)-α,β-γ,δ-dienoates have been prepared by the Reformatsky reaction on α-oxo ketene dithioacetals.[106b] Treatment of acyclic α-oxo ketene dithioacetals with ethyl bromoacetate and Zn in refluxing ether/benzene afforded the corresponding allylic alcohols in good yields. Difficulties were encountered with α-oxo ketene dithioacetals derived from cyclic ketones. Dehydration of the allylic alcohols (I_2, PhH, reflux, 0.5–1 h) afforded the δ,δ-bis(methylthio)dienoates (40–70%) while methanolysis of the carbinols [$BF_3 \cdot Et_2O$, CH_3OH] afforded propene-1,3-dicarboxylates (50–70%) in an alkylative 1,3-carbonyl transposition process.

Vinylogous thiol esters and α-oxo ketene dithioacetals undergo reaction with dimethylsulfonium methylide to afford a synthesis of butenolides and furans via an intermediate epoxide (Eq. 119, Table 27).[45,107–109] Treatment of α-oxo ketene dithioacetals with dimethylsulfonium methylide has also been reported to give the ring expansion products in low yield (6–19%).[108] Ketone enolate anions undergo 1,2-nucleophilic additions to α-oxo ketene dithioacetals and vinylogous thiol esters in low to moderate yields and this transformation can be effected more efficiently by utilizing hydrazone enolate anions in a two-step procedure.[31] The hydrazones are readily hydrolyzed [$Cu(OAc)_2$/THF–H_2O (NaOAc, AcOH, pH 4)]. Lastly, hydrazone formation has been observed upon treatment of α-oxo ketene dithioacetals with hydrazine.[52]

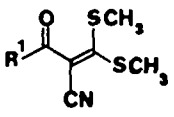
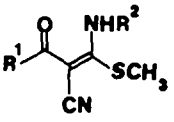
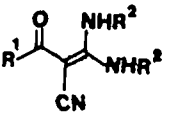
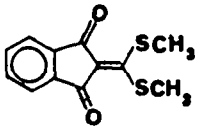
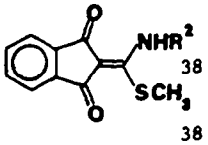
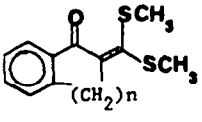
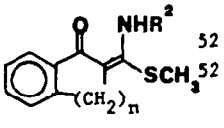
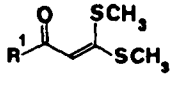
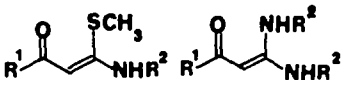
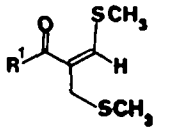
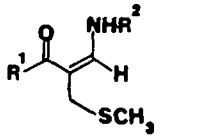
4. 1,4-CONJUGATE ADDITION REACTIONS

The conjugate addition of nucleophiles to vinylogous thiol esters and α-oxo ketene dithioacetals generally results in substitution via an addition–elimination pathway. A brief tabulation of the reactions of various nucleophiles with conjugated ketene dithioacetals has been reported.[4g] Many of the heterocyclic syntheses beginning from α-oxo ketene dithioacetals involve an initial substitution reaction proceeding by a 1,4-conjugate addition–elimination sequence.

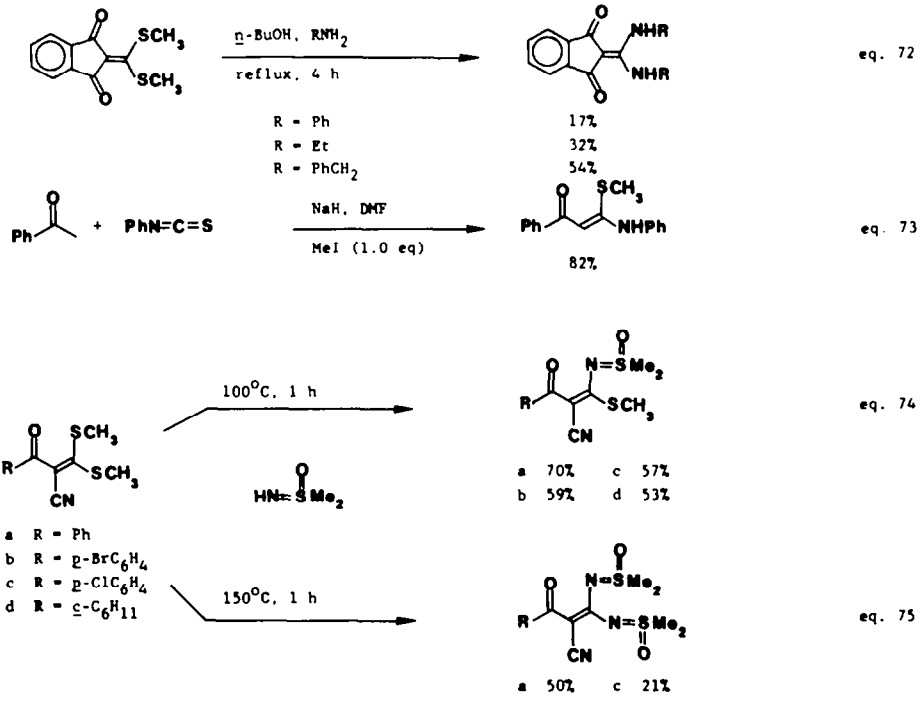
4.1. *Conjugate addition of heteroatom and enolate nucleophiles*

Gompper and Topfl[110] reported the addition of amines to various conjugated ketene dithioacetals to afford the corresponding conjugated ketene N,S-acetals (Eq. 71, Table 15) which could be converted

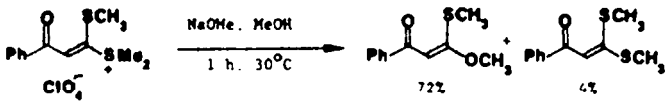
Table 15. Synthesis of ketene N,N- and N,S-acetals from α-oxo ketene dithioacetals and vinylogous amides from vinylogous thiol esters

Substrate	R^1 or n	Amine R^2NH_2	% Yield	Product(s)	Ref
	MeO	H	98		110
		Ph	98		110
		p-MeOPh	90		110
		β-$C_{10}H_7$	69		110
	Ph	H	85		113
		Et	89		113
		C_6H_{11}	50		113
		Ph	86		113
		p-$NO_2C_6H_4$	10		113
		p-$MeOC_6H_4$	54		113
	C_6H_{11}	Ph	40		113
	p-$MeOC_6H_4$		80		113
	p-BrC_6H_4		71		113
	2-furyl		50		113
	2-thienyl		30		113
	Ph	H	93		113
		Me	95		113
		Ph	63		113
	2-furyl	Ph	49		113
		Ph	83		38
		p-ClC_6H_4	73		38
		o-MeC_6H_4	78		38
		m-MeC_6H_4	58		38
		p-MeC_6H_4	39		38
		o-$MeOC_6H_4$	37		38
		m-$NO_2C_6H_4$	65		38
	1	Ph	50		52
	2	Ph	35		52
					
	Ph	Ph	40	10	112
		p-ClC_6H_4	31	11	112
	p-$MeOC_6H_4$	Ph	32	12	112
	p-BrC_6H_4	Ph	41	12	112
	p-Me C_6H_4	Me	80		118
		C_6H_{11}	83		118
	p-$MeOC_6H_4$	Me	75		118
		C_6H_{11}	82		118

into conjugated ketene aminals by reaction with a second equivalent of the same (Eq. 72)[38] or a different amine (Eq. 71).[4a] The procedure was extended by Junjappa and co-workers[111,112] and Augustin and co-workers[52,113] to α-oxo ketene dithioacetals for the synthesis of α-oxo ketene N,S-acetals which were subsequently exploited in a variety of heterocyclic syntheses. The less reactive α-oxo ketene dithioacetals generally afforded a mixture of the N,S-ketene acetals and the N,N-ketene aminals (Table 15), although use of morpholine afforded exclusively the ketene aminals.[112] The α-oxo ketene N,S-acetals can be converted into the corresponding ketene aminals, although higher reaction temperatures are generally required.[113] These results, coupled with the observations of Stachel,[54a] indicate that the order of reactivity of the ketene acetals toward nitrogen nucleophiles is O,S > S,S > N,S. Consequently, the best method for the preparation of α-oxo ketene N,S-acetals involves reaction of an enolate anion with an isothiocyanate followed by S-alkylation (Eq. 73),[18,19,21-23,112,114-116] or by S-alkylation of β-oxo thioamides.[117] Alternative approaches make use of the reactions of a β-chloro-β-alkylthio-α,β-enone with amines and of β,β-dichloroenones (CH_3SNa, pyrolidine, ether).[64b] Vinylogous thiol esters undergo a cleaner and higher yield reaction to afford the corresponding vinylogous amides (Table 15).[118] Generally a single or predominant stereoisomer is formed; although stereochemical assignments appear not to have been established. The structures of the ketene N,S-acetals arising from the ketene S,S-acetals are drawn with both the *E* and *Z* configuration although in general the *E* isomer is drawn for alkyl ketones and the *Z* isomer for aryl ketones. This is consistent with the reported stability of *E* and *Z* vinylogous thiol esters[46,60,63b,85b] and with the observed reactions of organocopper reagents with α-oxo ketene dithioacetals which proceed in a stereoselective fashion and presumably also involve an addition–elimination sequence.[46] Dimethylsulfoximide has also been used as the nitrogen nucleophile[119] and again the occurrence of a mono or bis substitution process is dependent upon the reaction temperature (Eqs 74 and 75).



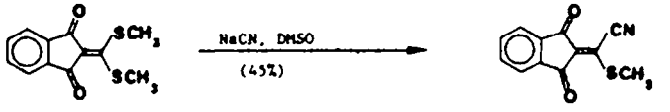
Heterocyclic compounds can be prepared directly by utilizing nucleophiles containing two heteroatoms (some combination of N, O, or S) that can effect a double substitution (Eq. 102). There are few reports on the utilization of oxygen nucleophiles aside from specific heterocyclic syntheses, although an intermediate α-oxo ketene O,S-acetal has been postulated in the conversion of α-oxo ketene dithioacetals into alkoxypyrimidines,[25] and alkoxypyrazoles[111] (e.g. Scheme 7). An interesting example of the use of an oxygen nucleophile, involves the conversion of a sulfonium derivative into the O,S-ketene acetal (Eq. 76).[120]



eq. 76

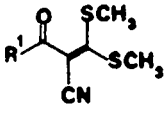
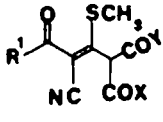
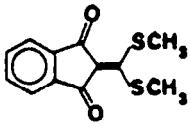
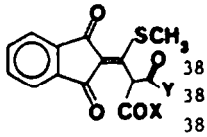
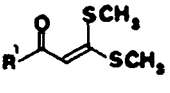
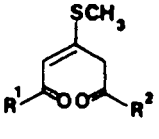
The Michael addition of enolates of active methylene compounds to carbonyl conjugated ketene dithioacetals has been reported by several workers[38,110,121] to occur in low to moderate yields (Table 16). More recently, Potts *et al.* have reported[17] the conjugate addition of ketone enolates to α-oxo ketene dithioacetals to afford 1,5-endiones containing an alkylthio substituent. The reaction used two equivalents of potassium t-butoxide in anhydrous THF to afford the potassium enolate of the 1,5-endione. This procedure prevented a second substitution reaction from occurring and aided in the purification process. Utilization of other bases or one equivalent of potassium t-butoxide gave lower yields and/or more complex product mixtures. These 1,5-endiones were subsequently exploited in syntheses of pyridines and pyrilium salts (Eqs 116–118).

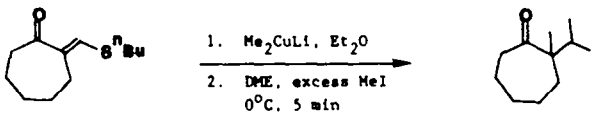
The conjugate addition of enolate anions of active methylene compounds to α-oxo ketene dithioacetals is an intermediate step in a synthesis of pyridones[27] (Eq. 110) and α-pyrones[24,122] (Table 28). Cyanide ion has also been used as a carbon nucleophile (Eq. 77).[38] Finally, β-sulfinyl-α,β-enones have also been employed as Michael acceptors (Eq. 127).[123]



eq. 77

Table 16. Reactions of conjugated ketene dithioacetals with enolate anions

Substrate	R^1	Enolate XCOCHMCOY or R^2COCH_2M X	Y or R^2	% Yield	Product	Ref
	MeO	Me	Me	84		110
		Me	Ph	58		110
		MeO	Me	95		110
		MeO	MeO	76		110
		MeO	NH_2	81		110
	Ph	Me	Me	55		121
		Me	Ph	36		121
		EtO	EtO	91		121
		MeO	MeO	28		38
		Me	Me	23		38
		Me	Ph	22		38
		NH_2	Ph	53		38
		CN	EtO	33		38
		Indan-1,3-dion-2-yl		59		38
	Ph		Ph	76		17
			2-thienyl	61		17
			2-pyridyl	58		17
	2-thienyl		2-thienyl	70		17
	2-furyl			47		17
	2-pyridyl		2-pyridyl	13		17
			2-thienyl	60		17
	m-BrC_6H_4		m-BrC_6H_4	81		17
	p-$MeOC_6H_4$		p-$MeOC_6H_4$	100		17
			Me	42		17
	2-thienyl		5-Cl-2-thienyl	75		17
	5-Br-2-thienyl		5-Br-2-thienyl	97		17



eq. 78

4.2. *Organocopper substitution reactions*

β-Alkylthio- and β,β-bis(alkylthio)-α,β-enones and enoates react with organocuprates to afford a substitution product in which an alkyl ligand from the organocopper reagent has replaced the alkylthio (arylthio) substituent. Coates and Sowerby first examined the reaction of organocopper reagents with vinylogous thiol esters to afford site-selective geminal alkylation via a double conjugate addition process[96a] and latter extended the reaction by trapping the intermediate enolate anion with electrophiles (Eq. 78).[124a] Various aspects of the reaction of β-alkylthio (or arylthio)-α,β-enones[75a,b,124–126] and enoates[30,62,67,126,127] with organocopper reagents were subsequently investigated by several workers (Table 17). Posner and Brunelle[126] showed that two different cuprate reagents could be employed in a sequential fashion, although it was difficult to stop the process after the initial substitution when the more reactive cuprates were employed. Kobayashi and co-workers[62,67]

Table 17. Reactions of β-alkylthio (or arylthio)-α,β-enones and enoates with organocuprates

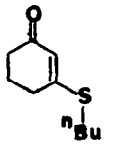
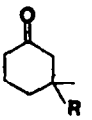
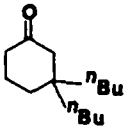
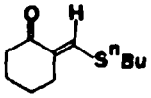
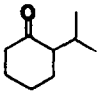
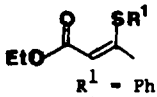
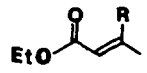
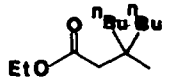
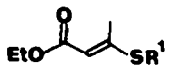
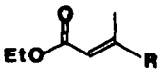
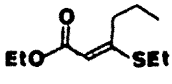
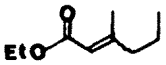
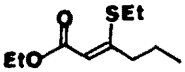
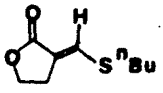
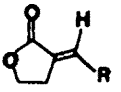
Substrate	Reagent (equiv)	Solvent	Rxn Cond	(E : Z)	% Yield (R)	Product	Ref
	A (1.1)	Et_2O	0°C, 0.5 h		84(Me)		126
	i. A (1.0)	Et_2O	-78°C, 0.5 h				
	ii. B (5.0)		-20°C, 1 h		80(n-Bu)		126
	B (1.1)	Et_2O	0°C, 0.5 h		90		126
	A	Et_2O	0°C		95		96a
							
R^1 = Ph	A (10)	Et_2O	0°C, 1 h		80 (Me)		126
R^1 = n-Bu	A (10)	Et_2O	0°C, 2 h		70 (Me)		126
R^1 = Ph	D (5.0)	THF	-78°C, 2 h	(<1:99)	79 (n-Bu)		62
							
	B (10)	Et_2O	-20°C, 2 h		95		126
							
R^1 = Et	E	THF	-78°C	(90:10)	96 (Et)		62
	D	THF	-78°C	(90:10)	94 (n-Bu)		62
	F	THF	-78°C	(90:10)	96 (n-C_6H_{13})		62
R^1 = Ph	D (5.0)	THF	-78°C	(>99:1)	94 (n-Bu)		62

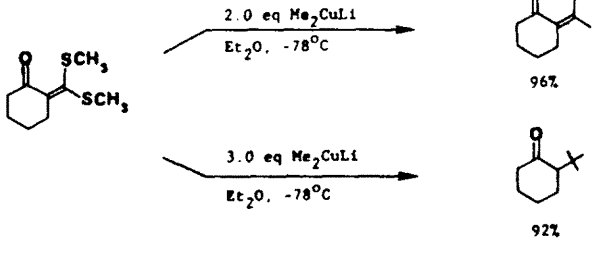
Table 17—*Continued*

Substrate	Reagent[a] (equiv)	Solvent	Rxn Cond	(E : Z)	% Yield (R)	Product	Ref
	G	Et_2O	25°C, 12 h	(50:50)	53		30
	G	THF	25°C, 12 h	(10:90)	72		30
	G	Et_2O	-78°C	(99:1)	99		30
	G	THF	0°C	(90:10)	82		30
	A				92(Me)		127
	B (1.1)	Et_2O	-78°C, 0.5 h		85(n-Bu)		127

[a] A = Me_2CuLi. B = $^nBu_2CuLi$. C = $CH_2{=}CCH_2CH_2MgBr$, CuI, n-Bu_3P.
D = n-BuMgBr, CuI. E = EtMgBr, CuI. F = n-$C_6H_{13}MgBr$, CuI. G = $(Me_2CuSCN)Li_2$.

investigated the copper catalyzed conjugated addition of Grignard reagents to β-alkylthio (or arylthio)-α,β-enoates and discovered that the substitution reaction proceeded stereospecifically with net retention of configuration for both the *E* and *Z* stereoisomers. The selectivity was slightly higher for the phenylthio substituent than for the alkylthio substituents, a result suggesting the importance of providing a group that will eliminate rapidly. Dieter and Silks[30] examined the reaction of these enoate substrates with lithium dialkylcuprates and again found the reaction to also proceed with retention of configuration, although the *E* substrate exhibited no stereoselectivity in Et_2O (Table 17). Later investigations by Dieter and Silks[30,125] showed that the reaction of β-alkyl substituted vinylogous thiol esters with organocopper reagents was stereoselective, but that the direction and degree of stereoselectivity was dependent upon several reaction parameters (Eqs 83–89). Martin and Moore exploited this reaction in their synthesis of α-alkylidene-γ-butyrolactones (Table 17) which could be converted into α,β-butenolides.[127]

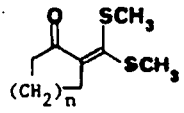
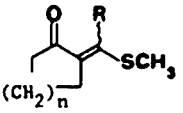
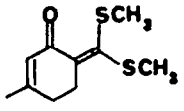
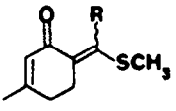
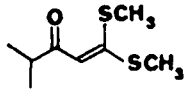
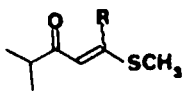
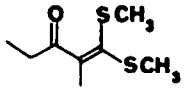
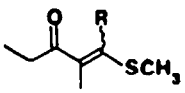
Corey and Chen[14] found that α-oxo ketene dithioacetals underwent a clean and high yield reaction with either two or three equivalents of an organocopper reagent to afford α-alkylidine or α-tertiary alkyl ketones, respectively (Eqs 79 and 80). This procedure has been employed in several synthetic applications for construction of the isopropylidine group.[128] Ittah and Shahak reported similar transformations for the α-dithiomethylene derivatives of diethyl malonate.[129] Dieter *et al.*[46] reinvestigated the reaction of organocuprates with α-oxo ketene dithioacetals (Table 18) and discovered that the reaction could be controlled to afford vinylogous thiol esters in a chemo- and stereoselective process. Although some degree of chemoselectivity could be achieved with the lithium dialkylcuprates by use of low reaction temperatures, the 3-methoxy-3,3-dimethyl-1-butynyl[130a] and the phenylthio[130b] mixed cuprates ($RL_{nt}CuLi$) proved to be more effective. These more thermally stable and less reactive cuprates containing non-transferable ligands provided a set of reagents that displayed significant differential reactivity with the α-oxo ketene dithioacetals and the product vinylogous thiol esters. In general, they were used in THF which is known to decrease the rate of organocopper



eq. 79

eq. 80

Table 18. Preparation of vinylogous thiol esters by the chemo- and stereoselective reactions of organocuprates with α-oxo ketene dithioacetals[46a]

Substrate	n	Cuprate Ligand R	Cuprate[a]	% Yield	(E : Z)	Product
	1	Me	A	81	(97:3)	
			B	96	(98:2)	
		n-Bu	A	83	(92:8)	
			B	55	(92:8)	
		sec-Bu	A	93	(97:3)	
		tert-Bu	A	96	(95:5)	
		c-C_3H_5	B	77	(70:30)	
	2	Me	A	75	(77:23)	
		n-Bu	A	70	(90:10)	
		sec-Bu	A	62	(79:21)	
		tert-Bu	A	96	(95:5)	
		Me	A	79	(94:6)	
		Me_2CH=$CHCH_2CH_2$	A	75	(96:4)	
		Me	A	87	(94:6)	
			B	51	(96:4)	
		n-Bu	A	69	(93:7)	
			B	93	(89:11)	
		sec-Bu	A	97	(94:6)	
		tert-Bu	A[b]	53	(20:80)	
		Me	A	88	(97:3)	
		n-Bu	A	47	(96:4)	

[a] A = (PhSCuR)Li. B = $(MeOCMe_2C{\equiv}CCuR)Li$. Reactions were run in THF unless otherwise noted. [b] Et_2O was used as solvent.

conjugate addition reactions. Undoubtedly, the chemoselectivity is a function of both the solvent and ligand on the organocuprate reactivity and this allows considerable experimental variation for solving problems that may arise with specific substrates. The acetylenic cuprate occasionally gave higher yields of vinylogous thiol esters but also gave products arising from reduction of the C—S bond. The phenylthio cuprates afforded poor results in diethyl ether because of low solubility of the reagent.

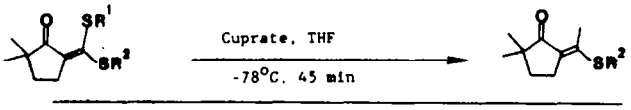
A series of organocuprate reagents was examined in order to explore the effect of a specific organocuprate reagent upon product distributions and stereoselectivity. Where solubility permitted, the substitution reaction was examined in THF, Et_2O, and PhH or $PhCH_3$ for the ketene dithioacetal of 4-phenylcyclohexanone. When 1.2 equivalents of organocopper reagent was utilized the more reactive cuprates, $(CH_3)_2CuLi$, $[(C_6H_{11})_2PCuCH_3]Li$, $[(CH_3)_2CuCN]Li_2$, and $[(CH_3)_2CuSCN]Li_2$ gave substantial quantities (> 14%) of 4-phenyl-2-isopropylidinecyclohexanone via a non-chemoselective bis-substitution reaction. The yield of the bis-substitution product increased along the solvent series THF, Et_2O, $PhCH_3$ when the first three cuprates were employed and decreased along the same solvent series for the latter cuprate. This is consistent with the general increase in the reaction rate of the organocopper conjugate addition process along the same solvent series; the results obtained with $[(CH_3)_2CuSCN]Li_2$ appears to be an exception. The mixed cuprates, $(PhSCuCH_3)Li$ and $(CH_3OCMe_2C{\equiv}CCuCH_3)$, afforded good yields of vinylogous thiol esters and low yields of the bis-substitution product, although the phenylthio mixed cuprate afforded poor yields in diethyl ether because of solubility problems. The phosphine complexed cuprates, $Ph_3P{\cdot}(CH_3)_2CuLi$ and $n\text{-}Bu_3P{\cdot}(CH_3)_2CuLi$, afforded good yields of vinylogous thiol ester in THF while the latter cuprate afforded increased yields of the bis-substitution product in Et_2O and $PhCH_3$. The lower order

cyanocuprate, $(CH_3CuCN)Li$, did not effect substitution under the reaction conditions. The stereoselectivity of the reaction showed some variation with organocuprate reagent and solvent and in general the *E*:*Z* distribution hovered around a 70:30 ratio. The influence of solvent was not uniform but depended on the specific organocuprate employed. The small range of isomer ratios obtained, however, suggest relatively small differences in transition state energies.

Reaction of α-oxo ketene dithioacetals with organocuprates afforded the *E* vinylogous thiol esters predominantly. An exception was noted with the acyclic substrates which afforded the *Z* stereoisomers upon reaction with the t-butylphenylthio cuprate. The observed stereoselectivities were generally high (> 90:10) although the 6-membered ring analogs displayed more modest selectivity (80:20–70:30). Equilibrium studies on the *E* and *Z* vinylogous thiol esters established that the isomer ratios obtained in the substitution reaction are determined by kinetic control of the product distributions. Examination of two α-oxo ketene dithioacetals containing different alkylthio substituents revealed that the alkylthio substituent *syn* to the ketone carbonyl was replaced in a stereospecific manner (Eq. 81). The reaction can best be understood in terms of an addition–elimination mechanism and the predominant formation of the *E* stereoisomers may reflect preferential motion of the alkylthio substituent *syn* to the ketone carbonyl away from the O atom and its attendant solvent shell. The direction of this motion can be rationalized on the basis of unfavorable steric or dipole interactions in the enolate intermediate. As the transferable ligand R increases in size from methyl or n-butyl to t-butyl, gauche butane interactions will influence rotomer distributions and these apparently favor formation of the *Z* stereoisomers in the reaction of several acyclic substrates with the t-butylcuprate.

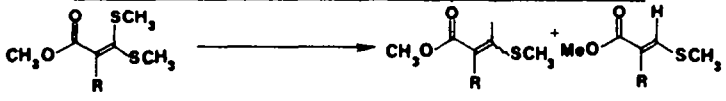
The corresponding ester analogs did not undergo the substitution reaction, but instead afforded primarily the product arising from reduction of the C—S bond (Eq. 82).[46] Introduction of a carbanion stabilizing substituent at the α-carbon atom suppressed this reduction pathway and favored the substitution reaction (Eq. 82).

The development of procedures for the facile conversion of α-oxo ketene dithioacetals to vinylogous thiol esters suggested the possibility of effecting a stereoselective synthesis of α,β-unsaturated ketones via the sequential addition of organocuprates to α-oxo ketene dithioacetals. The stereospecific organocopper substitution reactions of β-alkylthio-α,β-enoates[62,67] and an early investigation by Posner and Brunelle[126] on the ketone analogs suggested the feasibility of this approach. However, an extensive investigation by Dieter and Silks[125] revealed that the degree and direction of stereoselectivity was dependent upon a complex set of reaction parameters. This investigation examined vinylogous thiol esters containing primary, secondary, and tertiary β-alkyl substituents, and cuprates containing



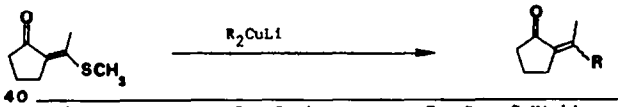
eq. 81

R^1	R^2	Cuprate	% Yield
Et	Me	Me_2CuLi	45
Me	Et		67
		(PhSCuMe)Li	64



eq. 82

R	Cuprate	Solvent	(E : Z)	% Yield	
H	Me_2CuLi	THF	13	61	
H	(t-BuCuSPh)Li	Et_2O	(94:6)	90	
PhS	(MeCuSPh)Li	THF	(24:76)	86	11
PhS	(n-BuCuSPh)Li	THF	(5:95)	84	



eq. 83

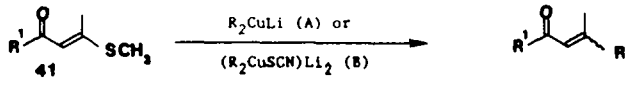
40

Cuprate	Rxn Cond	E : Z	% Yield	
n-Bu_2CuLi	Et_2O, -78°C	12:88	84	Inversion
	THF, -60°C	88:12	90	Retention
	THF, Me_2S, -78°C	90.2:9.8	78	Retention
t-Bu_2CuLi	Et_2O, Me_2S, -60°C	25:75	80	Inversion

primary, secondary, and tertiary transferable alkyl ligands. The role of solvent was also examined. This extensive investigation revealed that the substitution could proceed with either inversion or retention of configuration with the newly introduced β-alkyl substituent either on the same or opposite side of the double bond, respectively, than the alkylthio substituent which it replaced. Both the degree and direction of stereoselectivity was found to depend upon substrate structure, cuprate reagent, transferable ligand, solvent, and reaction temperature in a complex manner. In general, factors such as low reaction temperatures, highly reactive cuprates, and solvents that increase the rate of organocopper conjugate addition reactions were of paramount importance in obtaining a high degree of stereoselectivity. For this reason, highly reactive cuprates such as the lithium dialkylcuprates, the phosphidocuprates[131a] of Bertz and Dabbagh, and the higher order cuprates[131b] of Lipshultz *et al.* were employed.

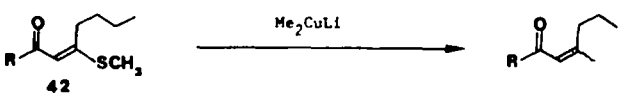
Reaction of cyclopentanone **40** with lithium di-n-butylcuprate in diethyl ether afforded the enone with net inversion of configuration while reaction in THF occurred with net retention of configuration (Eq. 83). This marked the first observation that the solvent could drastically alter the direction of stereoselectivity in these substitution reactions. Although good stereoselectivity was achieved, it was very sensitive to the reaction temperatures and could be improved by use of lower temperatures. The t-butylcuprate in Et_2O afforded modest selectivity with net inversion of configuration.

The acyclic substrates **41a, b** and **42a, b** gave results similar to those of **40** (Eqs 84 and 85). Reaction of **41a, b** with lithium di-n-butylcuprate proceeded with net inversion of configuration in Et_2O and with retention of configuration in THF to afford the enones in excellent yields and with excellent selectivity. The yields were slightly lower in the more powerful coordinating solvent THF. Substrates **42a, b** reacted with lithium dimethylcuprate with net inversion and retention of configuration in Et_2O and THF, respectively (Eq. 85). Here, the less reactive lithium dimethylcuprate afforded excellent yields and selectivities in Et_2O but only modest yields and poor selectivities in THF which decreases the rate of the conjugate addition reaction. In fact, removal of Et_2O, introduced from the ethereal solution of methyllithium used in the generation of the cuprate, resulted in almost no selectivity. The α′ substitution pattern of **41a, b** and **42a, b** had no bearing upon either the degree or direction of stereoselectivity when either lithium di-n-butyl or dimethylcuprate were employed. Methyl ketone **41a**, however, underwent reaction with a sec-butyl higher order cuprate with net retention while the isopropyl ketone **41b** underwent the substitution reaction with net inversion of configuration indicating that the α′ substitution pattern does affect the direction of selectivity when a cuprate containing a secondary alkyl transferable ligand is employed.



	R^1	Cuprate R	Rxn Cond	E : Z	% Yield	
a	Me	(A) n-Bu	Et_2O, -65°C	4 9 95.1	97	Inversion
			THF, -65°C	70 30	87	Retention
			THF, Me_2S, -78°C	97.4:2.6	93	Retention
		(B) sec-Bu	Et_2O, -55°C	92 8	60	Retention
		(A)	THF, Me_2S, -40°C	94:6	58	Retention
b	i-Pr	(A) n-Bu	Et_2O, -78°C	4:96	98	Inversion
		(A)	THF, Me_2S, -78°C	60:40	79	Retention
		(B)	Et_2O, -58°C	11:89	85	Inversion

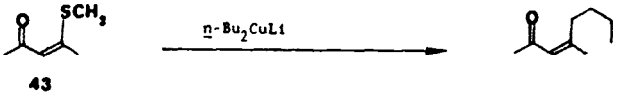
eq. 84



	R	Rxn Cond	E : Z	% Yield	
a	Me	Et_2O, -65°C	96:4	95	Inversion
		THF-Et_2O, -35°C	30:70	77	Retention
		THF, -65°C	46:54	76	Retention
b	i-Pr	Et_2O, -78°C	91:9	99	Inversion
		THF-Et_2O, -18°C	33:67	89	Retention

eq. 85

The *Z* vinylogous thiol ester **43** reacted with lithium di-n-butylcuprate in Et_2O and in THF with net retention of configuration (Eq. 86). This is in marked contrast to the *E* vinylogous thiol esters **41a, b** which reacted with lithium di-n-butylcuprate with net inversion in Et_2O and retention in THF. This observation is of considerable synthetic importance since it indicates that a mixture of *E* and *Z* vinylogous thiol esters will undergo reaction with cuprates containing a primary alkyl group in Et_2O to afford a single stereoisomer in a highly stereoselective fashion. The direction of selectivity is, however, influenced by a number of variables and not all combinations of substrate and cuprate possibilities are expected to yield this fortuitous and synthetically useful stereoselective but non-stereospecific process. In this instance, a confluence of factors favoring a stereospecific process is undesirable if the initial reaction of the α-oxo ketene dithioacetal with the organocopper reagent affords a mixture of *E* and *Z* vinylogous thiol esters.



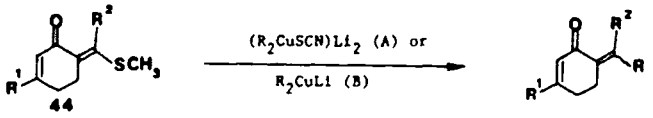
43

Rxn Cond	E : Z	% Yield	
Et_2O, -78°C	4:96	64	Retention
THF, -78°C	8:92	61	Retention

eq. 86

Cyclohexanone derivatives gave variable results with respect to the direction of selectivity with the results appearing to be more a function of the substrate and of the cuprate than of the solvent. In general, the vinylogous thiol esters derived from the α-oxo ketene dithioacetal of cyclohexanone afforded modest (70:30) stereoselectivities upon reaction with organocuprates. The reaction of 2-[1-(methylthio)ethylidine]cyclohexanone with $(t\text{-}Bu_2CuSCN)Li_2$ and reactions of the substrates containing a β-sec-butyl or β-t-butyl substituent with lithium dimethylcuprate, however, did afford excellent stereoselectivities (> 95:5). The cyclohexenone derivatives displayed more consistent patterns. The 3-methyl-2-cyclohexenone derivative **44a** reacted with a methyl higher order cuprate in Et_2O with net inversion while the 3-isopropoxy-2-cyclohexenone derivative **44b** reacted with lithium di-n-butylcuprate in Et_2O or THF with net retention (Eq. 87). It is noteworthy that the 3-alkoxy-2-cyclohexenone derivatives with a linear connectivity of the alkoxy substituent favorably disposed to electronically assist in the expulsion of the methylthio group undergo the substitution reaction with net retention of configuration in both Et_2O and THF. These 6-membered ring derivatives also generally afforded modest stereoselectivities in contrast to the acyclic and 5-membered ring analogs. Excellent selectivity was observed, however, for reaction of the 3-alkoxy derivative with a higher order cuprate in Et_2O. This solvent and cuprate combination, as expected, provides a maximum rate of reaction favoring retention of configuration.

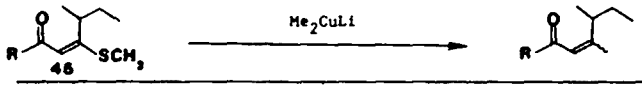
Acyclic substrates **45a, b** containing a β-sec-butyl substituent react with lithium dimethylcuprate in Et_2O with net inversion of configuration to afford the enones in high yields and with excellent selectivity (Eq. 88). The reaction of the same cuprate with **45a** in THF occurred with net inversion but with poor



44

	R^1	R^2	Cuprate R	Rxn Cond	E : Z	% Yield	
a	Me	$Me_2C{=}C(CH_2)_2$	(A) Me	Et_2O, -60°C	83:17	100	Inversion
b	Me_2CHO	Me	(B) n-Bu	Et_2O, Me_2S, -63°C	76:24	95	Retention
				THF, Me_2S, -30°C	77:23	98	Retention
			(A)	Et_2O, -60°C	92:8	100	Retention

eq. 87



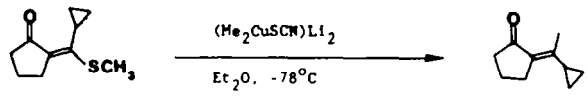
45

R	Rxn Cond	E : Z	% Yield	
Me	Et_2O, -50°C	96:4	80	Inversion
	THF, -78°C	55:45		Inversion
i-Pr	Et_2O, -50°C	96:4	78	Inversion

eq. 88

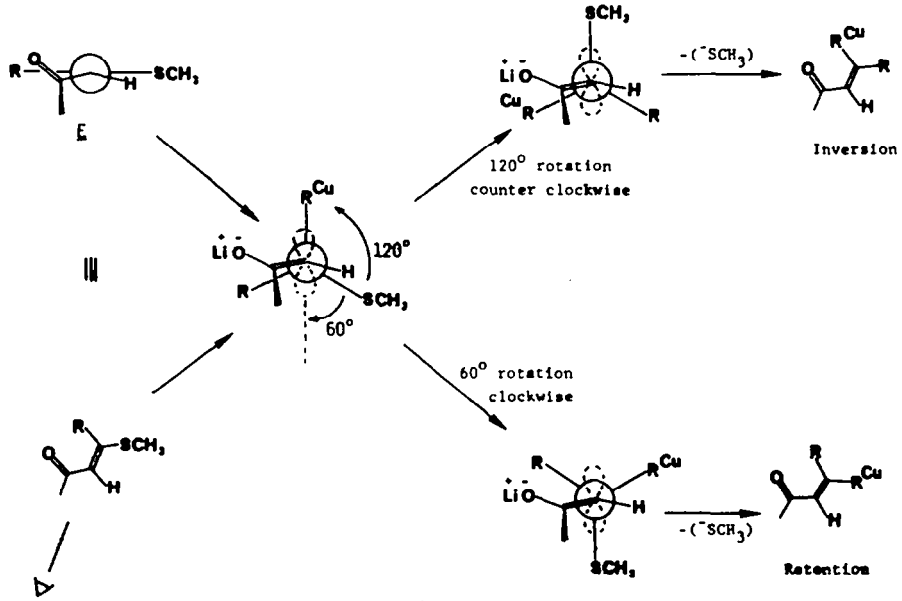
selectivity. Again, the α′-substitution of these substrates had no effect upon the degree or direction of the stereoselectivity when organocuprates containing primary alkyl ligands were employed.

Although this study demonstrated that the substitution reaction could be achieved with a high degree of stereoselectivity for the more reactive ketone substrates, two important points needed to be addressed from a synthetic perspective. First, could this methodology be employed for the stereoselective synthesis of α,β-unsaturated ketones from α-oxo ketene dithioacetals if both reactions exhibited modest selectivity? Second, in view of the sensitivity toward the reaction conditions involved in the reaction of the vinylogous thiol esters with organocuprates, could the reaction be carried out on a synthetically useful scale with a high degree of stereoselectivity? Conversion of a 70 : 30 *E* : *Z* mixture of vinylogous thiol esters to a 99 : 1 mixture of enones (Eq. 89) and conversion of 1.4 g of **42a** to the enone (with Me_2CuLi) in 92% yield as a 92 : 8 mixture of *E* and *Z* stereoisomers demonstrates the potential synthetic utility of the transformation despite the variability observed in both the degree and direction of stereoselectivity.



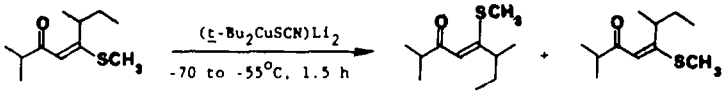
eq. 89

The observed stereoselectivities can be understood in terms of an addition–elimination mechanism. In this view rotomer distributions in an intermediate enolate anion will determine whether the reaction proceeds with inversion or retention of configuration and this interpretation is consistent with the sensitivity of the stereochemical outcome in extent and direction to reaction parameters such as substrate structure, cuprate reagent, temperature, and solvent. Conjugate addition of an organocuprate to an *E* vinylogous thiol ester will afford an intermediate enolate with a good leaving group at the γ-C atom. In order for this leaving group to be expelled there must be rotation about the γ-C atom so that the C—S bond of the leaving group can achieve a *trans*-periplanar relationship with the π-orbital of the enolate for facile elimination. Rotation of 60° leads to retention of configuration while a 120° rotation leads to inversion of configuration (Scheme 5). In the *Z* vinylogous thiol esters the minimum motion of 60° is consonant with motion of the alkylthio substituent away from the enolate O atom and its attendant solvent shell and retention of configuration is observed in either THF or Et_2O. The *E* vinylogous thiol esters generally undergo the reaction with inversion of configuration in Et_2O and retention in THF. Here, the more strongly coordinating solvent THF affords a freer more basic enolate favoring minimum motion leading to retention while the less effective coordinating solvent



Scheme 5.

Et_2O may allow S–Cu coordination which would of necessity require 120° rotation leading to inversion of configuration. In fact, isomerization of an *E* vinylogous thiol ester is observed when a t-butyl cuprate is employed (Eq. 90) and is consistent with S–Cu complexation. This isomerization occurs in Et_2O and not in THF and the *E* and *Z* vinylogous thiol esters yield an identical isomerization ratio upon treatment with the t-butyl cuprate. The inversion of configuration observed with the *E* isomers in Et_2O could also occur by initial isomerization to the *Z* isomer followed by conjugate addition–elimination with retention of configuration and this pathway cannot be ruled out. Nevertheless, neither model accounts for all the observed results which is indicative of the complexity of organocopper conjugate addition reactions in terms of cuprate structure, solvent dependent aggregation, and potentially multiple reaction pathways leading to products.



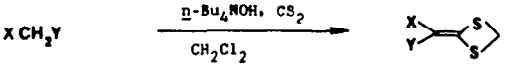
Solvent	Cuprate Equivalents	Isomer Ratio	
THF	2.0	0	: 100
Et_2O	0.1	5	: 95
	0.2	11	: 89
	2.0	83	: 17

eq. 90

5. HETEROCYCLIC SYNTHESIS

5.1. *1,3-Dithietanes, 1,3-dithiolanes, 1,3-dithianes, 1,2,4-trithiolenes, 1,2-dithioles, and α-dithiolylidene ketones*

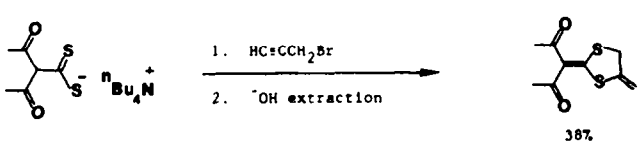
The 1,3-dithietanes,[7b,12b] dithiolanes,[10,14,18–20,23,32,34,38,41b,52] and dithianes[10b,19,20,23,38,41,52] can be prepared by alkylation of dithiolate dianions (derived from CS_2 alkylation of enolate anions) with 1,1-, 1,2-, and 1,3-bifunctional electrophiles, respectively (Eq. 91, Tables 1, 3 and 4). Low yields are generally obtained for the dithiolate dianions derived from simple acyclic[10] and 6-membered cyclic ketones[52] while moderate yields have been reported for an indanone derivative. Moderate to excellent yields of 1,3-dithiolanes and 1,3-dithianes have been obtained from aryl and heteraryl ketones[19] and from active methylene compounds.[20,23] These results indicate that attractive yields of dithiolanes and dithianes require dithiolate dianions of active methylene compounds or ketones having no α'-H atoms.



X	Y	% Yield
MeCO	MeCO	19
MeCO	PhCO	40
PhCO	PhCO	16

eq. 91

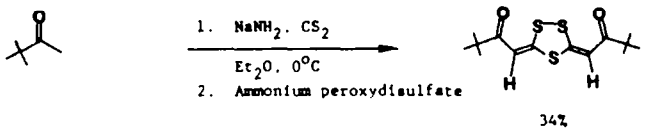
Although dihalides have generally been employed, 1,3-dithiolanes have been prepared from 2-methylthio-1,3-dithiolium cations[48] (Eq. 18, Scheme 1) and a 4-oxo-1,3-dithiolane has been synthesized using α-chloroacetamide as the electrophile.[35] A 4-methylene-1,3-dithiolane derivative was obtained when propargyl bromide was used as the alkylating agent and involved an intramolecular addition of the S heteroatom to the C≡C bond (Eq. 92).[12b]



eq. 92

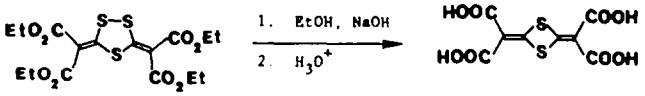
1,3-Dithietanes have also been prepared by the condensation of two molecules of an α-diazo ketone with CS_2 (Eq. 24).[53] The desaurins (Eq. 3) contain the 1,3-dithietane ring system and have been prepared under a variety of reaction conditions.[2c,5–7,34] These include pyrolysis of β-oxo dithioic acids,

their dianion metal salts, and the mono- or bis(S-benzoyl) ketene dithioacetals. They can also be prepared by oxidation (I_2, Br_2, ammonium peroxydisulfate) of β-oxo dithioic acids and the dithioate dianions derived from active methylene compounds. The oxidation conditions also afford 1,2,4-trithiolanes (Eq. 93) and the course of the reaction appears dependent upon substrate structure. This



eq. 93

route to trithiolanes was first reported by Wenzel[132] in 1900 and has been reexamined by several workers.[34,133] The dithiolate dianion derived from methyl cyanoacetate affords, upon oxidation, the trithiolane while the dithiolate dianion derived from methyl malonate affords the desaurin.[34] Interestingly, treatment of the trithiolanes with ethanolic NaOH[132b] or triethyl phosphite[53a] effects reductive desulfurization to afford the desaurins (Eq. 94). Consequently, oxidation procedures under



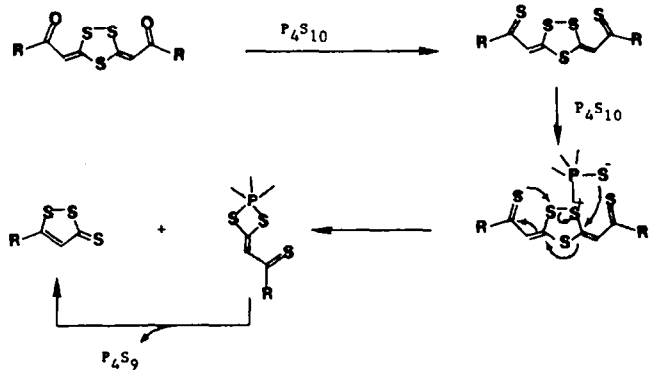
eq. 94

alkaline conditions may afford the desaurins via the trithiolanes. Treatment of the trithiolanes with P_4S_{10} yields 3-thione-1,2-dithioles[133] (Scheme 6) which can also be prepared from β-oxo dithioic acids and α-oxo ketene dithioacetals (Eq. 95)[10a] under similar reaction conditions (Table 19). The procedure works for a wide range of conjugated ketene dithioacetals[10,13,32b,40,134] in low to moderate yields. A mechanism for the reaction has been described.[134b]

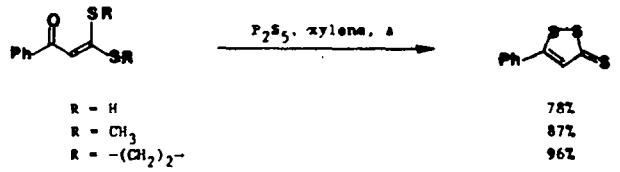
A review article reports[70b] extensive synthetic routes to the α-dithiolylidene ketones which are of interest because of the nature of the bonding in these molecules (*vide supra*).

5.2. *Thiophenes and thiazolines*

Two general strategies have been developed for the synthesis of thiophenes from conjugated ketene S,S- and N,S-acetals. The first involves the synthesis of a conjugated ketene dithioacetal containing an S-alkyl group (e.g. CH_3, CH_2CN, CH_2COR, CH_2CO_2R) that can undergo subsequent cyclization onto the conjugated functionality (e.g. CN, COR, CO_2R). The second strategy involves cyclization of the enamine moiety of ketene N,S-acetals onto an S-alkyl unit (e.g. $CH_2C{\equiv}C$, $CH{=}C{=}CH_2$).

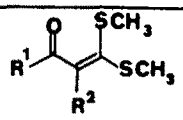
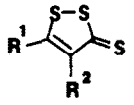
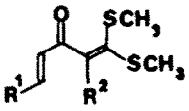
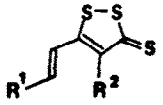
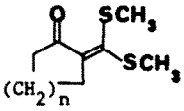
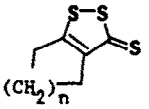
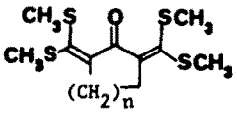
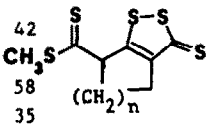
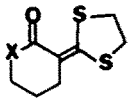
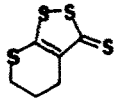
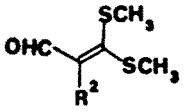
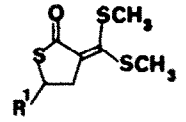
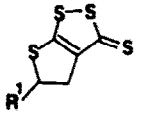


Scheme 6.

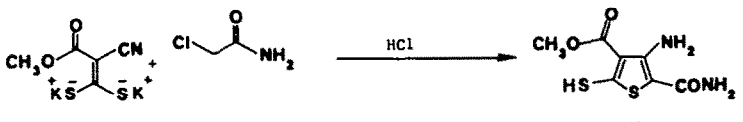


eq. 95

Table 19. Synthesis of 3-thione-1,2-dithioles

Substrate	R^1 or n	R^2 or X	% Yield	Product	Ref
	Me	Me	35		13a
	Me	Et	55		13a
	Et	Me	46		13a
	tert-Bu	H	64		13a
	n-Pr	Et	75		13a
	Ph	Me	10		13a
	p-$MeOC_6H_4$	Me	11		13a
	Ph	i-Pr	2		13a
	Ph	H	23		10b
	1		20		13b
	2		70		13b
	3		45		13b
	4		45		13b
	2		42		13b
	3		58		13b
	4		35		13b
		O	60		134a
		S	20		134a
		Et	26		40
		Ph	39		40
		p-$MeOC_6H_4$	58		40
		p-MeC_6H_4	58		40
		o-MeC_6H_4	40		40
	p-MeC_6H_4		21		32b
	p-$MeOC_6H_4$		21		32b
	2-thienyl		10		32b

Thiophene formation was observed during studies on the alkylation of dithioic acids or the monoanions derived from them. Gompper and Schafer[35] reported that alkylation of the dithioic acid derived from methyl cyanoacetate with α-chloroacetamide under acidic conditions yielded a thiophene arising from initial S-alkylation followed by closure onto the nitrile (Eq. 96). A similar procedure involving the S-alkylation of dithioic acid anions with α-chloroketones was observed to afford thiophenes (Eq. 23).[12b] The dithioic acid anion, however, was derived from acetylacetone and a mixture of thiophene and thienothiophene products were obtained in modest yields.

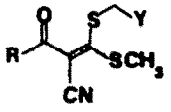
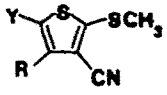
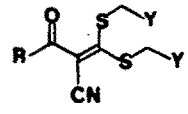
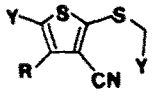
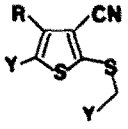
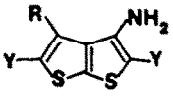
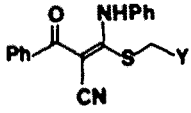
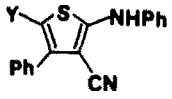


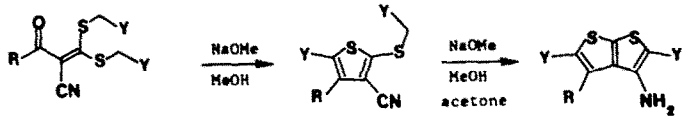
eq. 96

56%

Alkylation of dithiolate dianions derived from α-cyanoketones[21] with α-halo esters, nitriles, and ketones has been examined as a general route to thiophenes. The dithiolate dianions can be sequentially alkylated with CH_3I and XCH_2Y (Y = CN, COR, CO_2R) to afford mixed ketene dithioacetals or treated with two equivalents of the α-halocarbonyl or nitrile electrophile. The latter compounds can be converted in two steps into thienothiophenes (Eq. 97). Under these basic reaction conditions,

Table 20. Synthesis of thiophenes and thienothiophenes[21]

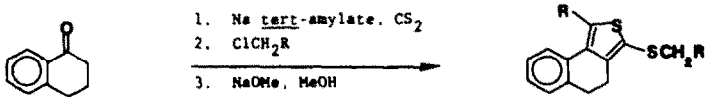
Substrate	R	Y	% Yield	Product
	Ph	CN	45	
	p-BrC_6H_4		41	
	p-$MeOC_6H_4$		20	
	2-furyl		23	
	2-thienyl		35	
	Ph	CO_2CH_3	45	
	p-BrC_6H_4		60	
	p-$MeOC_6H_4$		36	
	2-thienyl		21	
	Ph	CH_3CO	51	
	p-BrC_6H_4		33	
	p-$MeOC_6H_4$		30	
	2-furyl		63	
	2-thienyl		37	
	Ph	CN	30	
	Ph	CO_2CH_3	25	
	Ph	COPh	20	
	Ph	p-$NO_2C_6H_4$	74	
	p-ClC_6H_4	CO_2CH_3	47	
	Ph	CN	20	
	Ph	CO_2CH_3	57	
	Ph	$COCH_3$	28	
	2-thienyl	$COCH_3$	45	
		$COCH_3$	75	
		PhCO	79	
		p-BrC_6H_4CO	95	
		p-$NO_2C_6H_4$	21	



eq. 97

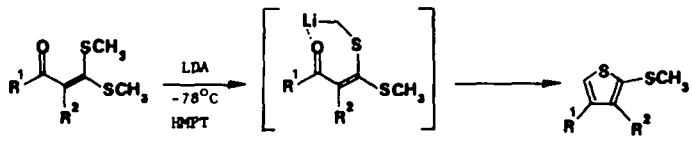
cyclization occurs onto the ester or ketone functionality instead of the nitrile and the thiophenes are formed in low to moderate yields (Table 20). This procedure has been extended to ketene N,S-acetals[19,21,114,135] which afford 2-aminothiophenes (Table 20) and to simple α-oxo ketene dithioacetals employing α-chloro esters, nitriles, and amides[52] (Eq. 98).

During an investigation of the behavior of α-oxo ketene dithioacetals toward deprotonation, it was discovered that some substrates underwent deprotonation at the methylthio group followed by an



eq. 98

R = CO_2Et 52%
R = CN 55%
R = $CONH_2$ 49%



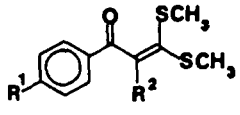
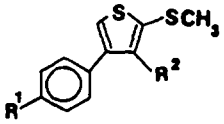
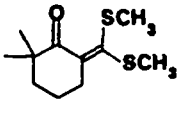
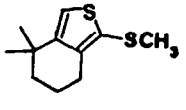
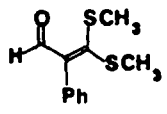
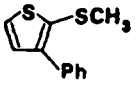
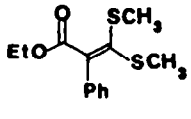
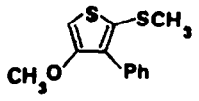
eq. 99

intramolecular aldol type condensation to afford thiophenes (Eq. 99).[78] Although thiophenes could be prepared from ketone, aldehyde, and ester conjugated ketene dithioacetals several structural limitations diminished the generality of the method (Table 21).[78b] The ketone cannot have any α'-H and substrates containing α-Me or H substituents undergo competitive deprotonation at these sites to afford the corresponding allyl and vinyl anions (Eqs 39 and 40). Ethylthio α-oxo ketene dithioacetals did not undergo the reaction and therefore the method is limited to the synthesis of 5-unsubstituted thiophenes, although this is not a major limitation since the 5-thienyl carbanions can easily be generated with strong bases. The yields were relatively modest and although considerable starting material was always recovered the yields could not be increased by utilization of two equivalents of base. α-Formyl ketene dithioacetals undergo reduction in the presence of LDA which did not occur with LTMP. Although limited in scope and efficiency, this methodology leads to 3,4-disubstituted thiophene derivatives which are not readily accessible. Utilization of ester substrates presents a rapid and useful approach to 4-hydroxythiophenes or 4-methoxythiophenes, if the reaction is quenched with methyl iodide, in modest yields.

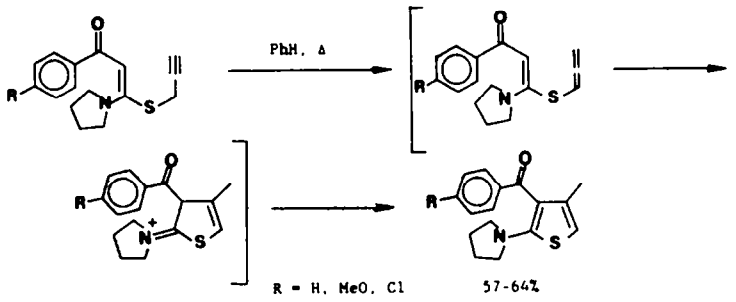
A more recent approach[117] to thiophenes involves alkylation of β-keto thioamides with propargyl halides. The resultant ketene N,S-acetals afford an intermediate allene which undergoes intramolecular alkylation of the enamine moiety under the thermal reaction conditions to afford 2-amino-3-acyl-4-methylthiophenes in good overall yields (Eq. 100). The reaction appears not to have been extended to the homologous propargylic halides to form different 4-alkyl substituents. Ketones containing α'-H were not examined.

Utilization of a secondary thioamide instead of a tertiary thioamide provides a route to N-alkyl or N-aryl thiazoline derivatives (Eq. 101).[116] Here, cyclization onto the allene occurs by nucleophilic

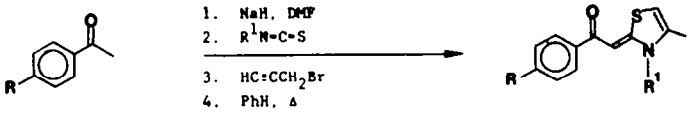
Table 21. Synthesis of thiophenes from α-oxo ketene dithioacetals[78b]

Substrate		Base	% Yield	Product
				
R^1	R^2			
H	Et	LDA[a]	55	
H	H	LDA	30	
MeO	H	LDA	30	
Ph	MeO	LDA	42	
		LDA	26	
		LDA	22	
		LTMP[b]	45	
		LDA	38	

[a]LDA = lithium diisopropylamide. [b]LTMP = lithium tetramethylpiperidide.



eq. 100



eq. 101

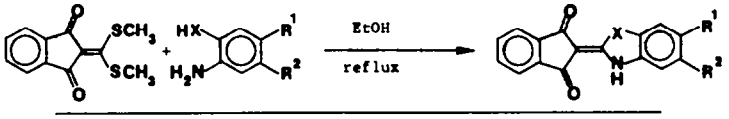
R	R^1	% Yield
H	Ph	71%
	Et	67%
MeO	Et	72%
Cl	Et	69%

addition of the N-atom of the enamine ambident nucleophile. The reaction also works for conjugated ketene N,S-acetals derived from acetylacetone and other active methylene derivatives and the overall yields are very good.

5.3. *Imidazolidines, oxazolidines, and thiazolidines*

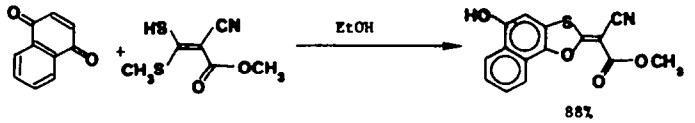
These 5-membered ring heterocyclic compounds containing two heteroatoms in the 1 and 3 positions are readily synthesized by reaction of α-oxo ketene dithioacetals with 1,2-diamines, 1,2-amino alcohols, and 1,2-amino thiols, respectively (Eq. 102).[52,110,113,136] The aliphatic bifunctional nucleophiles lead to simple heterocyclic ring systems while the aromatic heteroatom nucleophiles afford annulated poly-aromatic heterocyclic ring systems. These substitution reactions proceed by two sequential conjugate addition–elimination reactions similar to those described for simple amines (Eqs 71 and 72, Table 15).

An alternative strategy involves the alkylation of a conjugated ketene dithio hemi-acetal followed by intramolecular substitution. For example, Gompper and Schafer[35] reported the conjugate addition of a methyl dithioester to *p*-naphthoquinone followed by a conjugate addition of the *o*-hydroxy substituent and elimination of methanethiolate to afford the annulated thiazolidine (Eq. 103). Thiazolidines have also been prepared via this strategy by reaction of β-oxo dithioesters with aziridines.[34,113] The reaction proceeds by aziridine alkylation of the thiocarbonyl followed



eq. 102

X	R^1	R^2	% Yield
NH	H	H	40
O	H	H	37
S	H	H	51
NH	OMe	OMe	25
O	NO_2	H	37

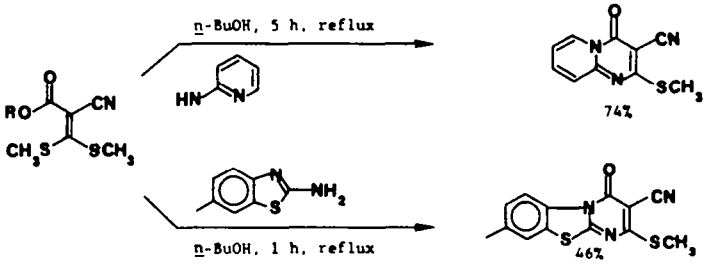


eq. 103

by an intramolecular substitution involving the N-atom in a conjugate addition–elimination sequence. Thiazolidines have also been prepared by alkylation of thioamides with bifunctional electrophiles.[18,19,21,115]

5.4. *Pyrimidines*

Pyrimidines have been obtained from α-oxo ketene dithioacetals and from vinylogous thiol esters. The general procedure involves reaction of a 1,3-dinitrogen nucleophile with a β-alkylthio- or β,β-bis(alkylthio)-α,β-unsaturated carbonyl compound in a sequential conjugated addition–elimination reaction to afford vinylogous amides or ketene N,S-acetals, respectively. These intermediates can undergo intramolecular 1,2-nucleophilic addition to the carbonyl to afford pyrimidines. The methodology exhibits considerable versatility for the synthesis of a variety of substituted pyrimidines and possesses some interesting limitations. The original exploitation of this strategy involved the synthesis of annulated pyrimidines (Eqs 104 and 105).[110]

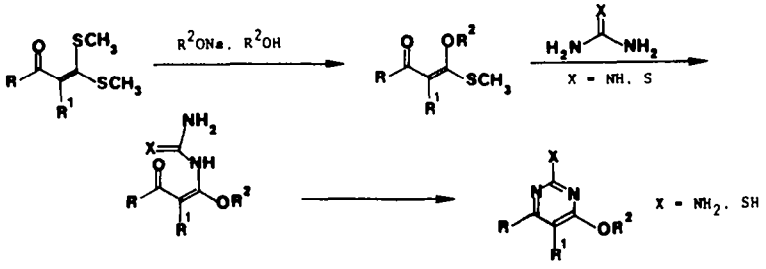


eq. 104

eq. 105

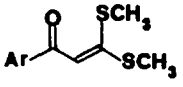
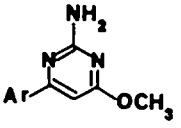
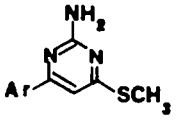
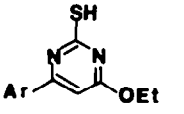
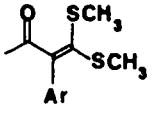
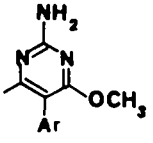
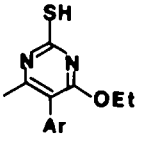
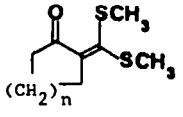
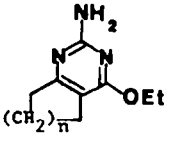
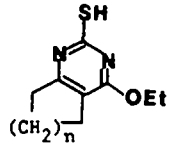
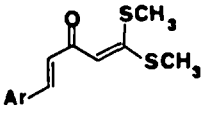
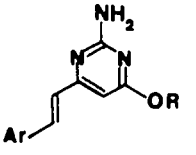
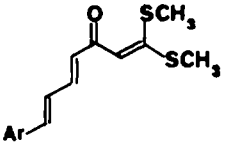
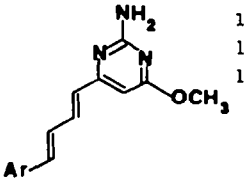
Subsequently, Junjappa and co-workers extended the generality of this strategy by using guanidine and thiourea as the nucleophilic reagents.[25,26,118,137,138] Reaction of α-unsubstituted β,β-bis(alkylthio)-α,β-enones with guanidinium nitrate in refluxing methanolic sodium methoxide affords the 2-amino-4-methoxy pyrimidines while utilization of thiourea affords the corresponding 2-mercapto-4-alkoxy analogs (Scheme 7, Table 22).[18,25] This procedure is particularly useful for the synthesis of the latter compounds, which would be difficult to prepare by alkylation of a free hydroxy group in the presence of the thiol functionality. These procedures have been extended to α-aryl substituted β,β-bis(alkylthio)-α,β-enones and to α-oxo ketene dithioacetals derived from cyclic ketones.[25a] Similarly, 6-styryl and 6-(4-aryl-1,3-butadienyl)pyrimidines have been prepared from the appropriate styryl and butadienyl substituted α-oxo ketene dithioacetals.[137] This procedure has also been used with ketene dithioacetals derived from α-cyanoketones utilizing guanidine or S-alkylisothioureas in a slight modification.[139]

The reaction is believed to proceed by an initial substitution of an alkylthio group by the alkoxide anion to afford an intermediate ketene O,S-acetal which then undergoes reaction with guanidine or thiourea to afford a ketene O,N-acetal (Scheme 7). The ketene O,N-acetal can undergo intramolecular cyclization to the pyrimidine. Although 4-alkylthio pyrimidines can be converted into 4-alkoxy pyrimidines by the action of metal alkoxides, the 4-alkylthio derivatives were never isolated from the reaction medium. This observation coupled with the fact that α-oxo ketene dithioacetals are less reactive than the corresponding ketene O,S-acetals with nitrogen nucleophiles strongly supports the assumption of an α-oxo ketene O,S-acetal intermediate. In one instance however, the reaction took a different course. Here, reaction of the ketene dithioacetal of cyclohexanone and thiourea gave the 1,3-uritidino-3-thione derivative via a bis-substitution reaction. 2-Amino- and 2-mercapto-4-alkylthio



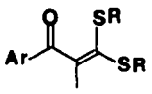
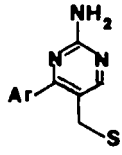
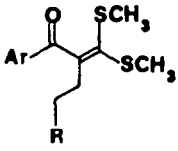
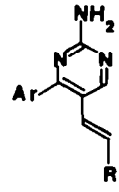
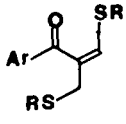
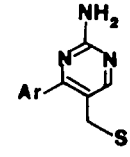
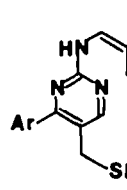
Scheme 7.

Table 22. Synthesis of pyrimidines from α-oxo ketene dithioacetals

Substrate	Ar or n	ROH	Rxn Cond	% Yield	Product	Ref
	Ph	Me	A	70		25b
	p-MeC_6H_4	Me	A	60		25b
	p-$MeOC_6H_4$	Me	A	64		25b
	Ph		B	50		25b
	p-MeC_6H_4		B	54		25b
	p-$MeOC_6H_4$		B	50		25b
	Ph	Et	C	60		25b
	p-MeC_6H_4	Et	C	83		25b
	p-$MeOC_6H_4$	Et	C	85		25b
	Ph	Me	A	40		25a
	p-ClC_6H_4	Me	A	35		25a
	p-$MeOC_6H_4$	Me	A	46		25a
	Ph	Et	C	34		25a
	p-ClC_6H_4	Et	C	33		25a
	p-$MeOC_6H_4$	Et	C	33		25a
	1	Et	A	56		25a
	2	Et	A	54		25a
	3	Et	A	46		25a
	1	Et	C	50		25a
	3	Et	C	44		25a
	Ph	Me	A	74		137
	p-ClC_6H_4	Me	A	62		137
	p-$MeOC_6H_4$	Me	A	66		137
	p-$Me_2NC_6H_4$	Et	A	68		137
	Ph	Me	A	62		137
	p-MeC_6H_4	Me	A	60		137
	p-$MeOC_6H_4$	Me	A	62		137

[a] A = NaOR, ROH, guanidine nitrate, reflux. B = NaH, DMF, guanidine nitrate, reflux. C = i. NaOR, ROH, thiourea, reflux ii. glacial acetic acid, reflux, 5 min.

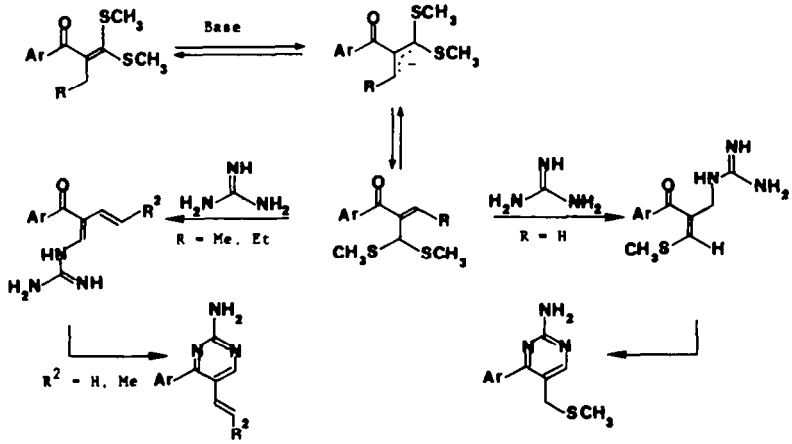
Table 23. Synthesis of pyrimidines from α-alkyl-substituted β-alkylthio- and β,β-bis(alkylthio)-α,β-enones

Substrate	Ar	R	Rxn Cond[a]	% Yield	Product	Ref
	Ph	Me	A	55		26
	Ph	Et	A	50		26
	Ph	$PhCH_2$	A	31		26
	p-$MeOC_6H_4$	Me	A	35		26
	Ph	H	A	22		26
	p-$MeOC_6H_4$	H	A	20		26
	Ph	Me	A	28		26
	p-$MeOC_6H_4$	Me	A	23		26
	Ph	Et	A	70		118
	p-ClC_6H_4	Me	A	75		118
	Ph	Me	B	65		118
	Ph	Et	B	60		118
	p-MeC_6H_4	Me	B	56		118
	p-$MeOC_6H_4$	Me	B	64		118

[a] A = NaOEt, EtOH, guanidine nitrate, reflux 10-12 h. B = NaH, DMF/PhH, guanidine nitrate, 80-85°C.

pyrimidines can be prepared from α-oxo ketene dithioacetals if the reaction is carried out with NaH in DMSO, although yields are significantly lower (33–35%).[25]

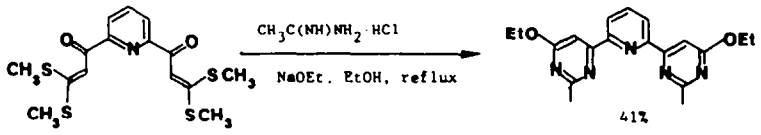
β,β-Bis(alkylthio)-α,β-enones containing an α-alkyl substituent undergo base-promoted isomerizations prior to reaction with guanidine. α-Methyl substituted substrates yield 5-alkylthiomethyl substituted pyrimidines while α-ethyl and propyl substituted substrates afford 5-alkenyl pyrimidines (Table 23).[26] The base-promoted isomerizations generate reactive intermediate allylic dithioacetals and vinylogous thiol esters from the methyl and alkyl substituted substrates as indicated in Scheme 8. 2-Amino pyrimidines have been prepared from vinylogous thiol esters ob-



Scheme 8.

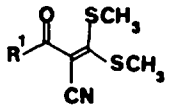
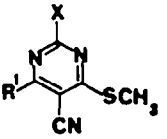
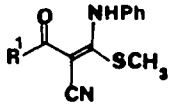
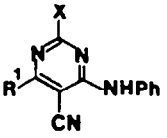
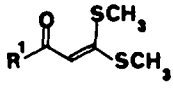
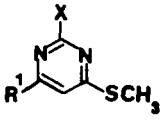
tained by base-promoted rearrangement of α-oxo ketene dithioacetals (Table 23).[118] Utilization of NaH in DMF heated to reflux affords pyrimidines arising from two molecules of vinylogous thiol ester and one molecule of guanidine.[118] The procedure is limited, however, since the starting vinylogous thiol esters were obtained in low yields (Eq. 41). This methodology has been extended to α-oxo ketene dithioacetals derived from fused heterocyclic systems (e.g. thiopyran-4-ones, thiepin-5(2H)-ones, and 1-N-(*p*-tolylsulfonyl)-2,3-dihydro-4(1H)-quinolones).[138]

Rudorf and Augustin[139] and Potts *et al.*[140] have reported a pyrimidine synthesis employing amidines and ketene dithioacetals derived from α-cyanoketones and aryl or heteraryl ketones (Eq. 106), respectively (Table 24).



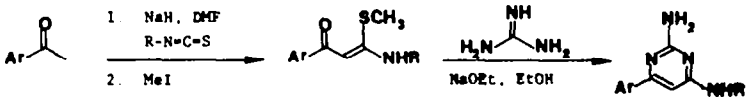
eq. 106

Table 24. Synthesis of pyrimidines from conjugated ketene dithioacetals and amidines

Substrate	R^1	$H_2NC(NH)X$ X	Rxn Cond[a]	% Yield	Product	Ref
	Ph	Me	A	91		139
	p-ClC_6H_4	Me	A	61		139
	2-furyl	Me	A	56		139
	2-thienyl	Me	A	69		139
	Ph	Ph	A	56		139
	p-ClC_6H_4	Ph	A	60		139
	Ph	p-$NO_2C_6H_4$	A	69		139
	Ph	Me	A	52		139
	Ph	Ph	A	63		139
	Ph	2-thienyl	B	45		140
	2-furyl	2-thienyl	B	23		140
	2-thienyl	2-thienyl	B	32		140
	2-pyridyl	Ph	B	33		140
	2-pyridyl	2-thienyl	B	44		140
	2-pyridyl	2-pyridyl	B	10		140
	2-pyridyl	3-pyridyl	B	37		140
	2-pyridyl	4-pyridyl	B	67		140

[a] A = Et_3N, DMF, amidine·HCl, reflux. B = NaH, PhH/DMF, amidine·HCl, 60°C to reflux.

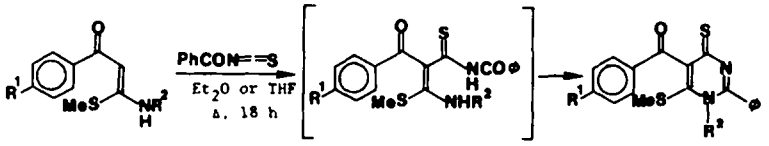
Pyrimidines have also been prepared from conjugated ketene N,S-acetals by two different procedures. The ketene N,S-acetals are treated with an alkaline ethanolic solution of guanidine to afford the pyrimidines in a procedure analogous to that described above (Eq. 107).[112] Reaction of β,β-



eq. 107

Ar	R	% Yield	% Yield
Ph	Ph	82	35
p-$MeOC_6H_4$	Ph	74	34
p-BrC_6H_4	Ph	84	45
Ph	p-ClC_6H_4	76	50
Ph	Et	70	40

bis(alkylthio)-α,β-enoates with primary amines affords intermediate ketene N,S-acetals which can be converted into 2,6-diamino-4-oxopyrimidines upon treatment with guanidine in a sodium ethoxide–ethanol solution heated to reflux.[112] This has been extended to the reaction of ketene N,S-acetals derived from α-cyanoketones with amidines (Table 24), guanidine, and S-alkylisothioureas.[139] Reaction of amidine with a ketene S,N-(sulfoximide)acetal affords an interesting 4-sulfoximide substituted pyrimidine.[141] Alternatively, the ketene N,S-acetals can react as enamines with isothiocyanates to afford 4-thioxopyrimidines (Eq. 108).[142] Here, heterocyclic ring formation occurs between the enamine unit and the isothiocyanate leaving the conjugated carbonyl functionality intact.



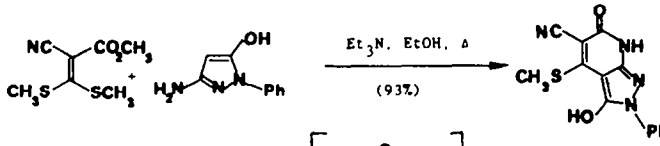
R^1	R^2	% Yield
H	Et	68 (THF)
Cl	Et	70
OMe	Et	68
Me	Et	67

eq. 108

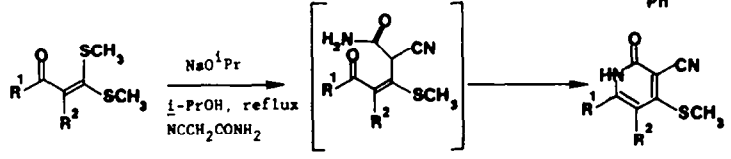
5.5. *Pyridones*

Pyridones can also be prepared from conjugated ketene acetals by a two-step process. First, substitution occurs via a sequential conjugate addition–elimination substitution reaction. This is followed by an intramolecular cyclization of a nitrogen nucleophile onto the carbonyl functional group to afford the simple or annulated pyridone ring system. This strategy was first implemented by Gompper and Topfl.[110] They combined carboalkoxy conjugated ketene dithioacetals with 3-amino-5-hydroxypyrazoles to afford annulated heterocyclic systems containing the pyridone ring system (Eq. 109).

Junjappa and co-workers[27,143] developed a synthetic route to 3-cyano-4-alkylthiopyridones by reaction of α-oxo ketene dithioacetals with cyanoacetamide in alkaline alcoholic medium (Eq. 110).



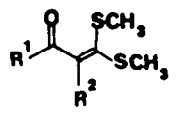
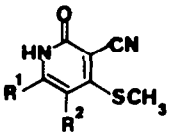
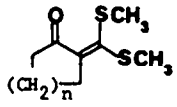
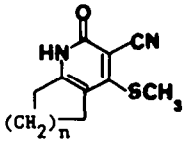
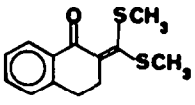
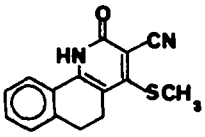
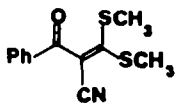
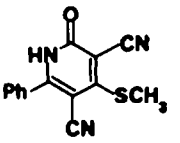
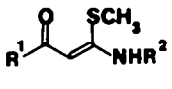
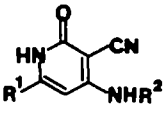
eq. 109



eq. 110

Utilization of sodium ethoxide afforded an inseparable mixture of 4-ethoxy and 4-methylthio pyridones. The 4-ethoxy derivatives presumably arise from intermediate α-oxo ketene O,S-acetals and this process can be suppressed by utilization of sodium isopropoxide. However, the 4-alkoxy derivatives were not readily prepared when two equivalents of sodium isopropoxide were employed. The methodology appears to be very general and moderate to good yields are obtained for α-oxo ketene dithioacetals having no α'-H (Table 25). Methyl ketones containing the α-oxo ketene dithioacetal functionality afford pyridones in moderate yields. The α-oxo ketene dithioacetals of cyclopentanone and cyclohexanone give pyridones in good yields, although the yield drops very rapidly for the higher homologue, cycloheptanone (30%). β,β-Bis(alkylthio)-α,β-enones containing an α-methyl or α-alkyl (e.g. Et, n-Pr) substituent underwent base-promoted isomerization prior to pyridone ring formation to afford 3-cyano-4-methylthiomethyl- and 3-cyano-4-alkenyl-pyridones in moderate to low yields, respectively (Eq. 111).[27] These results parallel those observed for pyrimidine formation from these substrates (Scheme 8). The synthesis of pyridones from ketene dithioacetals of active methylene

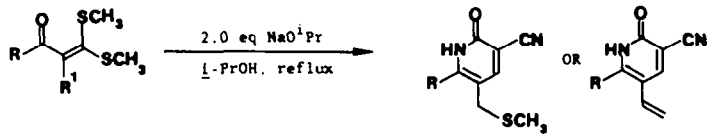
Table 25. Synthesis of pyridones from conjugated ketene dithioacetals and N,S-acetals

Substrate	R^1 or n	R^2	% Yield[a]	Product	Ref
	Me	H	65		143
	Ph	H	82		143
	p-MeC_6H_4	H	85		143
	3-pyridyl	H	65		143
	4-pyridyl	H	65		143
	Me	Ph	48		27
	Me	p-$MeOC_6H_4$	48		27
	1		76		27
	2		77		27
	3		30		27
			65		143
			82		122
	Ph	Ph	64		146
	p-ClC_6H_4	Ph	71		146
	p-$MeOC_6H_4$	Ph	62		146
	Ph	Et	55		146
	p-ClC_6H_4	Et	62		146
	p-$MeOC_6H_4$	Et	59		146

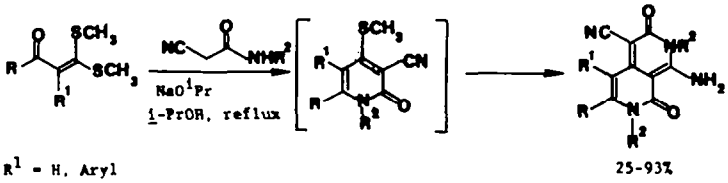
[a]Reaction Conditions = NaO^iPr, i-PrOH, reflux, H_2NCOCH_2CN.

compounds by this procedure has been reported.[122,144] Utilization of secondary α-cyanoacetamides generally results in a double cyclization involving substitution of the 4-methylthio substituent of the pyridone ring by a second molecule of the α-cyanoacetamide (Eq. 112).[145]

The procedure has been extended to the α-oxo ketene N,S-acetals which give rise to 3-cyano-4-aminopyridones in moderate to good yields.[146] Although α-oxo ketene N,N-acetals react with dimethyl acetylene dicarboxylate to afford pyridones, the ketene N,S-acetals yield only the enamine addition product and do not undergo cyclization to the pyridone.[147]



eq. 111



eq.112

Table 26. Synthesis of pyrazoles from cyano-α-oxo ketene dithioacetals

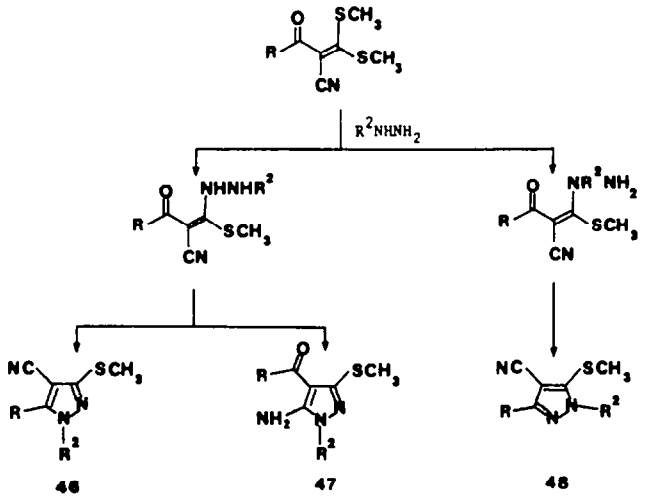
Substrate R	H_2NNH_2	H_2NNHPh		$H_2NNHC_6H_4$-p-NO_2		H_2NNHCH_3
	% Yield					
	46	**46 + 47**		**46 + 47**		**48**
Ph	77	60		21	61	96
4-ClC_6H_4	91	31	44		77	95
4-BrC_6H_4					47	71
2-furyl	52	54				

5.6. *Pyrazoles, isoxazoles, and thiazoles*

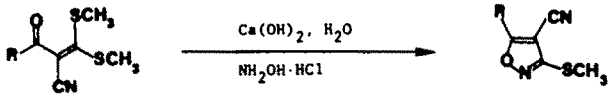
Gompper and Topfl reported[148] that conjugated ketene dithioacetals derived from active methylene compounds underwent reaction with hydrazines and hydroxylamines to form pyrazoles and isoxazoles, respectively. The reaction again involves a sequential substitution of one of the alkylthio groups by the N-atom followed by intramolecular addition of the N- or O-atom to the carbonyl carbon. Chauhan and Junjappa subsequently examined[111] the reaction of hydrazine with α-oxo ketene dithioacetals to give 5(3)-alkylthio pyrazoles (88–90%). Treatment of the α-oxo ketene dithioacetals with sodium ethoxide prior to reaction with hydrazine afforded the 5(3)-alkoxypyrazoles (60–67%) via the intermediate α-oxo ketene O,S-acetals. Rudorf and Augustin studied[149] the reaction of ketene dithioacetals of α-cyanoketones with hydrazines. Several different pyrazoles were generated since unsymmetrical hydrazines can undergo the initial conjugate addition reaction with either N atom and subsequent cyclization can occur onto either the nitrile or ketone (Scheme 9, Table 26). The hydrazine and methylhydrazine adducts cyclize onto the ketone functional group to afford 4-cyanopyrazoles **46** and **48** while the phenylhydrazines give adducts that cyclize onto either the ketone or nitrile to give pyrazoles **46** and **47**. Vinylogous thiol esters have also been converted into pyrazoles upon reaction with hydrazine in ethanol.[118]

A similar reaction of conjugated ketene dithioacetals with hydroxyamine gave the corresponding isoxazoles (Eq. 113).[149] Reaction of conjugated ketene N,S-acetals with hydroxylamine affords 3-aminoisoxazoles.[149,150] A ketene S,N-(sulfoximide)acetal has been converted into the corresponding 5(3)-sulfoximide substituted pyrazole and 3-sulfoximide substituted isoxazole by reaction with hydrazine and hydroxylamine, respectively.[141]

Reaction of α-oxo ketene N,S-acetals with thionyl chloride in pyridine affords thiazoles (Eq. 114). The reaction fails when R^3 is an alkyl group and is therefore limited to benzyl amines.[151]

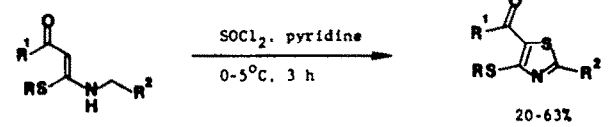


Scheme 9.



R	% Yield
Ph	70
2-ClC6H4	45
2-furyl	68

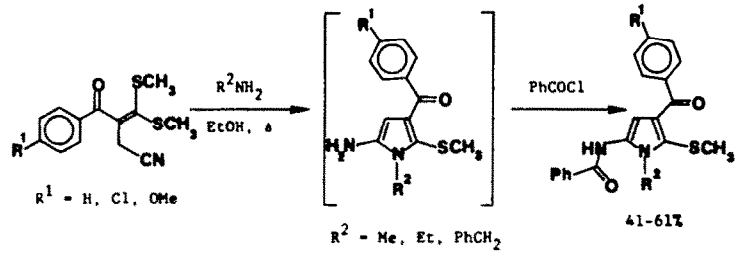
eq. 113



eq. 114

5.7. *Pyrroles*

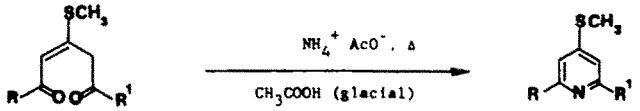
Apparao, Ila, and Junjappa have reported a synthesis of 2-amino-N-alkyl substituted pyrroles from α-cyanomethyl-β,β-bis(alkylthio)-α,β-enones and aliphatic amines. Only aromatic ketones were examined and the yields were moderate (Eq. 115).[28] These 2-amino-pyrroles were unstable and were isolated as their N-benzoyl derivatives.



eq. 115

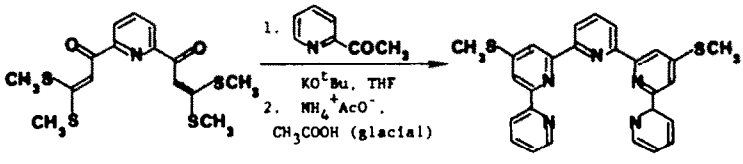
5.8. *Pyridines*

α-Oxo ketene dithioacetals have been used in a synthesis of 1,5-endiones by reaction with ketone enolates (Table 16). These 1,5-endiones can be converted into pyridines[17,29a] (Eqs 116 and 117) and pyrylium[152] (Eq. 118) salts. The latter procedure also constitutes a synthesis of thiopyrylium and

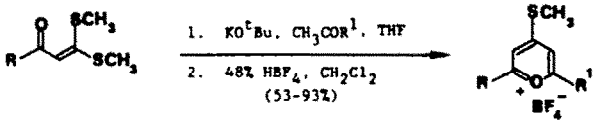


R	R^1	% Yield
Ph	Ph	81
4-MeOC6H4	4-MeOC6H4	85
Ph	2- pyridyl	89
2-furyl	2-thienyl	79
2-thienyl	2-thienyl	99
2-thienyl	5-Cl-2-thienyl	72
4-MeOC6H4	Me	70

eq. 116



eq. 117



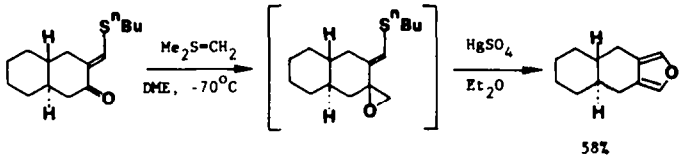
eq. 118

selenopyrylium salts since these are readily prepared from the pyrylium salts. The intermediate 1,5-endiones can be isolated. Alternatively, the two reactions can be conveniently carried out in a "one pot" process. The conjugate addition of ketone enolate anions to α-oxo ketene dithioacetals occurs in generally moderate yields with lower yields coming from ketone enolates containing α'-H. Optimal yields were obtained when two equivalents of potassium t-butoxide was employed. The second equivalent of base reacts with the product 1,5-endione to afford a potassium enolate stable toward further reactions. Isolation of these air-sensitive potassium enolates facilitates purification of the reaction mixture; the 1,5-endiones can be readily obtained upon neutralization. Other bases such as NaH proved less effective while sodium ethoxide afforded β-keto esters and α-pyrones. The strategy is sufficiently versatile that simple and annulated pyridines as well as polypyridinyls can be synthesized. Since in principle either component ketone can serve as the enolate or the α-oxo ketene dithioacetal unit, versatility is built into the procedure for maximizing yields. In general, higher yields are obtained when the aromatic ketone is utilized as the α-oxo ketene dithioacetal unit. This synthetic route to 2,6-furyl or thienyl substituted pyridines has been exploited in the synthesis of macrocyclic polyether diesters containing these heterocyclic units.[153]

1,5-Endiones can also be prepared by exploiting the chemoselective reaction of organocuprates with α-oxo ketene dithioacetals or α,β-unsaturated thiol esters coupled, respectively, with the 1,3-carbonyl transposition methodology of vinylogous thiol esters and α-oxo ketene dithioacetals employing hydrazone enolate anions. Although this strategy requires an additional step, it could prove more flexible in terms of substitution patterns and range of substituents that can be accommodated.

5.9. *Furans, butenolides, unsaturated lactones, α-pyrones and 1-thia-4-pyranones*

Synthesis of furans, butenolides, and α,β-unsaturated lactones from vinylogous thiol esters and α-oxo ketene dithioacetals involves the 1,2-nucleophilic addition of carbanions containing a protected or masked oxygen nucleophile that can participate in a subsequent cyclization process. Garst and Spencer[107] reported a furan synthesis from vinylogous thiol esters in 1973. The reaction involved the addition of dimethylsulfonium methylide to the vinylogous thiol ester to afford an intermediate allylic epoxide which underwent cyclization and elimination of methanethiol upon treatment with $HgSO_4$ (Eq. 119). The reaction does not work when the ylide is generated from the iodide salt and requires utilization of trimethylsulfonium fluoroborate as the ylide precursor. In one instance the epoxide could be isolated in 81% yield and quantitatively converted into the furan upon treatment with $BF_3 \cdot Et_2O$.

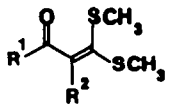
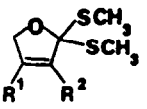
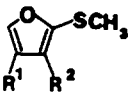
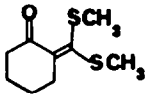
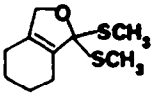
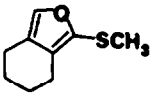
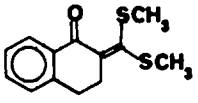
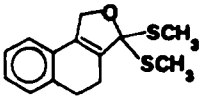
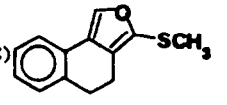
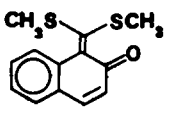
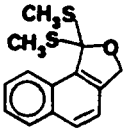
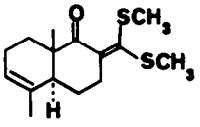
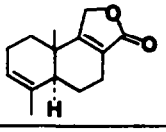


eq. 119

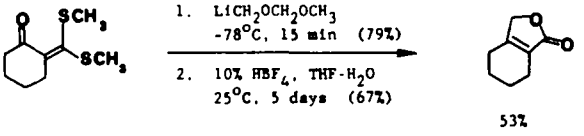
The reaction of dimethylsulfonium methylide with α-oxo ketene dithioacetals was subsequently reported by three groups (Table 27).[45,108,109] Ireland[109] employed this reaction in the construction of an annulated butenolide in a synthesis of triptolide and triptonide while Okazaki *et al.*[45] reported a more extensive investigation of the reaction. While Ireland had obtained the butenolide by treatment of the reaction mixture with aqueous HCl–MeOH, Okazaki *et al.* were able to obtain the corresponding cyclic dithio ortho ester. Although these ortho esters could be isolated, they could not be purified and were readily converted into 2-methylthiofurans by treatment with HCl, CH_3I, or by passage through a florisil column. The reaction gives best results in THF and shows more complex mixtures in DME and ether. Reaction of the ylide proceeds faster with the α-oxo ketene dithioacetals than with the vinylogous thiol esters. In an additional consideration, the 2-methylthio substituent on the furans derived from α-oxo ketene dithioacetals provides versatile synthetic opportunities since it can serve as a blocking group, undergo direct alkyl substitution with Grignard reagents and a Ni catalyst, be hydrolyzed back to a butenolide, or simply be removed by Raney Ni desulfurization. These procedures have been exploited in syntheses of the naturally occurring furans perillene and fosefuran.

Butenolides can also be prepared by the addition of alkoxy stabilized carbanions, which in turn are generated from the corresponding organotin compounds, to α-oxo ketene dithioacetals (Eq. 120).[154] Although formally equivalent for the synthesis of butenolides, this methodology can be expanded to the synthesis of 5-alkyl substituted butenolides from α-oxo ketene dithioacetals and a variety of aldehydes.

Table 27. Synthesis of dihydrofurans, furans, and butenolides from α-oxo ketene dithioacetals

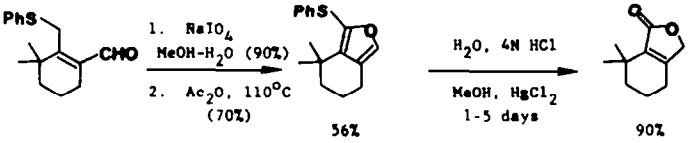
Substrate	% Yield[a]	Dihydrofuran	% Yield[b]	Furan	Ref
					
R^1 = Ph, R^2 = H	92		91 (A)		45a
R^1 = Me, R^2 = H			35 (B)		45a
R^1 = H, R^2 = Ph			51 (B)		45a
R^1 = $Me_2C{=}CH(CH_2)_2$, R^2 = H	83		61 (A)		45a
R^1 = CH_3, R^2 = $Me_2C{=}CH(CH_2)_2$			81[c]		45a
	97		72 (B)		45a
	92		89 (C)		45a
	71				45a
			84[d]		109

[a]Reaction Conditions: $Me_2S{=}CH_2$, THF, -70°C to room temperature.
[b]A = catalytic 2M HCl, room temperature. B = Florisil Column Chromatography.
C = MeI, H_2O, 56°C. [c]This furan was obtained from the intermediate epoxide.
[d]i. $Me_2S{=}CH_2$, THF/DMSO, -10°C to 25°C ii. 1:6 6M aqueous HCl-MeOH, 25°C, 15 h.

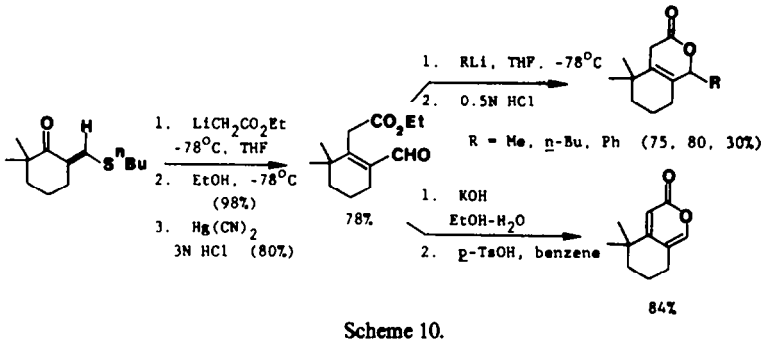


eq. 120

This methodology involving the addition of Grignard or organolithium reagents containing a protected hydroxy group or the unprotected alkoxide can be exploited in preparing larger ring lactones. Although δ-lactones have been prepared by a three-step procedure involving the 1,2-addition of ester enolates to α-oxo ketene dithioacetals the overall yields were low because $LiAlH_4$ reduction of the β-hydroxy esters resulted in considerable retro-Claisen like reactions occurring.[154] γ-Phenylthio-α,β-unsaturated aldehydes derived from vinylogous thiol esters (Table 12) have been exploited in a synthesis of the regioisomeric butenolides (Eq. 121).[100b] Butenolides have also been prepared by



eq. 121



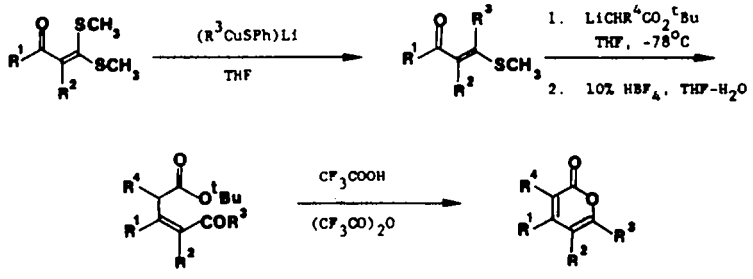
Scheme 10.

quenching the vinyl anion generated from methyl 2-methyl-3-phenylthiopropenoate (e.g. see Eqs 44 and 45) and the vinyl dianion obtained from the corresponding carboxylic acid with aldehydes.[81] The vinyl anion obtained from 2-methyl-3-phenylthiopropenoic acid underwent a similar reaction with ketones.[81b]

The addition of ester enolates to vinylogous thiol esters has been utilized in a synthesis of δ-lactones and α-pyrones (Scheme 10).[98] The procedure involves 1,2-nucleophilic addition of the ester enolate to a vinylogous thiol ester followed by acid-catalyzed rearrangement to afford the unsaturated aldehyde. The Rathke type addition reaction of ester enolates to the vinylogous thiol ester must be quenched at low temperatures or considerable retro-Claisen type cleavage occurs and starting materials are recovered. Addition of organolithium reagents to the aldehyde carbonyl affords an alkoxide intermediate that can undergo intramolecular lactone formation. Yields are good despite the possibility of proton abstraction in these systems. Enol lactonization under acidic conditions affords the corresponding α-pyrones.

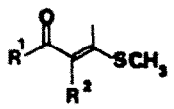
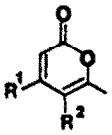
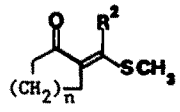
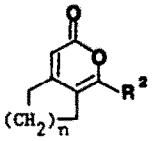
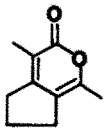
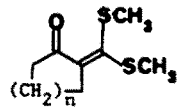
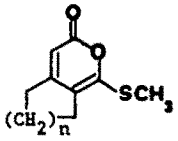
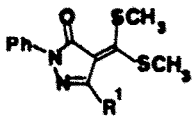
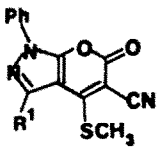
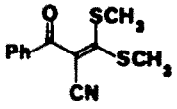
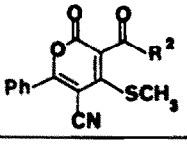
Dieter and Fishpaugh[99] have made use of their chemoselective substitution reaction of organocuprates with α-oxo ketene dithioacetals coupled with the 1,3-carbonyl transposition methodology involving vinylogous thiol esters in an α-pyrone synthesis employing a similar strategy (Scheme 11, Table 28). The strategy and methodology are sufficiently versatile that the alkyl substitution pattern at all four of the olefinic carbon atoms of the α-pyrone ring system can be systematically altered simply by choice of α-oxo ketene dithioacetal, organocuprate, and ester enolate. Alternatively, the 1,3-carbonyl transposition reaction of α-oxo ketene dithioacetals could be employed to afford a γ-carboalkoxy-α,β-unsaturated thiol ester which can be converted to a γ-keto ester upon reaction with organocuprates. Utilization of vinylogous thiol esters affords 6-alkyl substituted α-pyrones while addition of ester enolates to α-oxo ketene dithioacetals leads to 6-alkylthio substituted α-pyrones.[31] Ketone enolates can also be utilized although yields are somewhat lower in the 1,2-nucleophilic addition process. This problem can be solved by relying on hydrazone enolate anions. Although an additional step is required to hydrolyze the hydrazones, this step proceeds in excellent yields.[31] α-Pyrones have also been prepared by 1,4-conjugate addition of sodium cyanoacetate to α-oxo ketene dithioacetals followed by intramolecular cyclization (Table 28).[24,122]

Ketones containing α- and α′-methylene groups can be converted into 1-thia-4-pyranone derivatives (Eqs 4, 12 and 13)[8,10b,13a,44] upon treatment with base and CS_2. α,β-Unsaturated ketones undergo reaction with base and CS_2 at the α′-methylene group and intramolecular cyclization can occur to afford 5,6-dihydro-1-thia-4-pyranones[22] (Eq. 122). The cyclization can also be effected from 1,1-bis(alkylthio)-3-oxo-1,4-butadienes by heating a dioxane solution of the α-oxo ketene dithioacetal

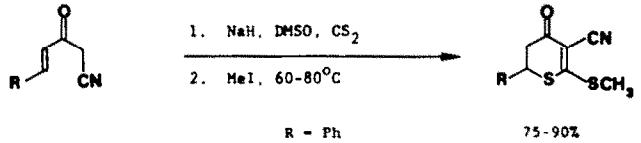


Scheme 11.

Table 28. Synthesis of α-pyrones from vinylogous thiol esters and α-oxo ketene dithioacetals

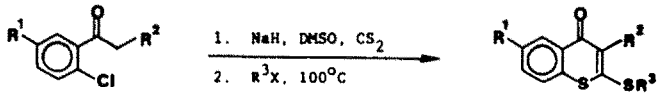
Substrate	R^1 or n	R^2	Enolate[a]	δ-Keto Acid[b] or Ester[c] % Yield	α-Pyrone	% Yield	Ref
	i-Pr	H	A	93[c]		92	99
	Et	Me	A	90[b]		90	99
	1	Me	A	88[c]		93	99
			B	72[b]		88	99
		sec-Bu	A	71[b]		99	99
	2	Me	A	74[c]		94	99
			B	77[b]		70	99
	2	Me	C	57[c]		83	99
	1		A	87[c]		93	31
	2		A	76[c]		85	31
	Me		D			65	24
	p-$MeOC_6H_4$					81	24
	p-MeC_6H_4					86	24
	p-ClC_6H_4					70	24
		OEt	E			54	122
		Ph	F			35	122

[a] A = $LiCH_2CO_2{}^tBu$. B = $LiCH_2CO_2SiMe_3$. C = $LiCH(CH_3)CO_2{}^tBu$. D = $NaCH(CN)CO_2Et$. E = $KCH(CN)CO_2Et$. F = NaCH(CN)COPh.
[b] δ-Keto Acid [c] Ester



eq. 122

in the presence of benzyl alcohol.[155] *o*-Chloroaryl ketones undergo similar cyclization reactions when heated in the presence of base and CS_2 to give 2-alkylthio-1-thia-4-chromones[18,115] (Eq. 123) after alkylation.



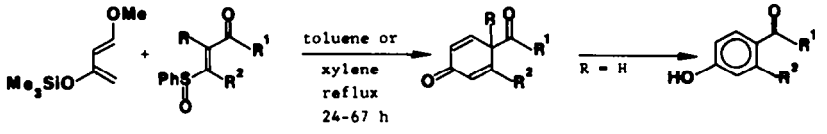
R^1	R^2	R^3	% Yield
H	H	Me	80
Cl	H	Me	82
Cl	H	$PhCH_2$	94
H	CN	$MeCOCH_2$	69
		$PhCOCH_2$	56
		p-$NO_2C_6H_4CH_2$	76

eq. 123

6. PERICYCLIC REACTIONS

6.1. *Diels–Alder reactions*

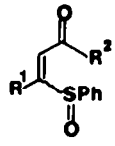
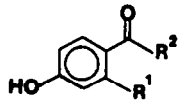
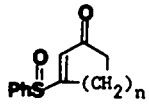
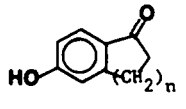
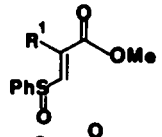
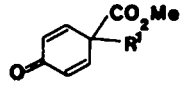
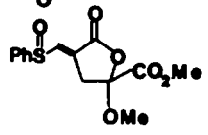
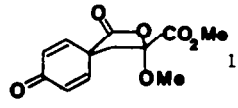
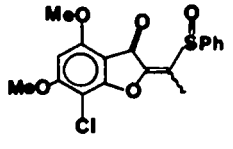
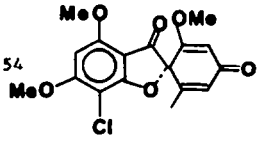
α-Oxo ketene dithioacetals and vinylogous thiol esters can, in principle, serve as dienophiles in a Diels–Alder reaction. The products would have a 6-membered ring containing two or one alkylthio (or arylthio) substituents that could be exploited in subsequent synthetic transformations. Danishefsky and co-workers[58,156] examined this strategy in a synthetic approach to cross-conjugated cyclohexa-2,5-dienones and phenols. Although the β-phenylthio-α,β-enones and enoates were not sufficiently dienophilic, the corresponding β-phenylsulfinyl derivatives entered into the Diels–Alder reaction in moderate to good yields after prolonged reaction times in benzene or toluene heated to reflux (Eq. 124, Table 29). Under the thermal conditions of the Diels–Alder reaction a sulfoxide *syn*-elimination occurred to afford the corresponding cyclohexadienones or phenols directly. This strategy was employed in the synthesis of disodium prephenate[156b] and of the antifungal agent griseofulvin.[156c] In the griseofulvin synthesis, an intermediate cyclohexadienone was prepared by this procedure and hydrogenated to control the stereochemistry in the substituted cyclohexenone moiety of the target molecule.



eq. 124

Both α-oxo ketene dithioacetals[106a] and vinylogous thiol esters[105] have been converted into Diels–Alder dienes either by reaction with Wittig reagents or by conversion into the corresponding silyl enol ethers. The 1,1-bis(alkylthio)-1,3-butadienes are poor dienes and afford Diels–Alder adducts only with the more reactive dienophiles such as maleic anhydride.[157] The corresponding 1-alkylthio-1,3-butadiene unit has also been generated but appears not to have seen wide synthetic application.

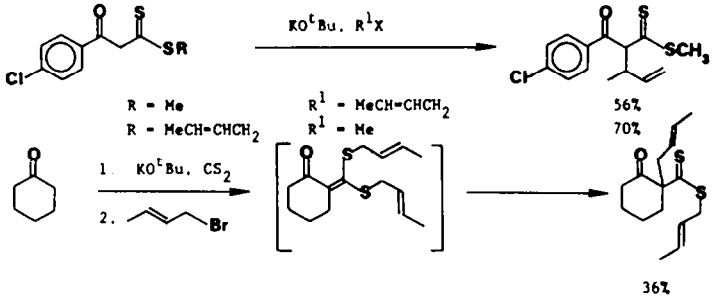
Table 29. Synthesis of phenols and 2,5-cyclohexadienones from β-phenylsulfinyl-α,β-enones and enoates

Substrate	R or n	R^2	Diene[a]	% Yield	Product	Ref
	Me	Me	A	75		58
	CH_2CO_2Me	OMe	A	42		58
	1		A	90		58
	2		A	68		58
	Me		A	83		58
	$CH_2C(OMe)_2CO_2Me$		A	58		58
			A	53-60		156b
			B	54		156c

[a] A = $MeOCH{=}CHC(OSiMe_3){=}CH_2$. B = $(MeO)_2C{-}CHC(OSiMe_3){=}CH_2$.

6.2. *Sigmatropic rearrangements*

Conjugated ketene dithioacetals containing S-allyl, S-crotyl, or S-propargyl substituents readily undergo the thio-Claisen rearrangement.[11,12] The mixed S-crotyl, S-methyl ketene dithioacetals rearrange to afford α-1-methylallyl-β-oxodithio esters (Eq. 125) while the symmetrical ketene dithioacetals afford α-crotyl-β-oxodithioesters indicative of a series of sigmatropic rearrangements involving the thiocarbonyl of the dithio ester and the second S-crotyl substituent (Eq. 126). These [3,3]sigmatropic rearrangements can occur at room temperature depending on the functionality in conjugation with the ketene dithioacetal [relative rates for ketene dithioacetals derived from active methylene compounds, XCH_2—(Y), display the following order: CO_2Et (CO_2Et) > COMe (CO_2Et) > COMe (COMe) > CO_2Et (CN) > COPh (COMe) > COPh (COPh) > CN (CN)] and the substitution pattern of the S-allyl group (allyl > crotyl). Consequently, alkylation of conjugated ketene dithiolate dianions with allyl halides generally affords mixtures of ketene dithioacetals and α-allyl dithio esters arising from the thio-Claisen rearrangement. For the less reactive substrates thermal cleavage generates allyl radicals and provides an undesired decomposition pathway. Similar alkylation of α-oxo ketene N,S-acetals results in a thio-Claisen rearrangement to afford α-allyl thioamides.



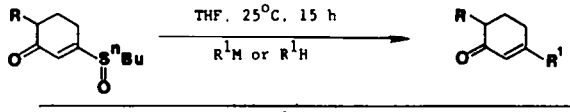
eq. 125

eq. 126

7. MISCELLANEOUS REACTIONS

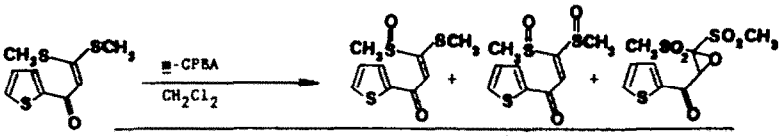
Several useful and interesting reactions have been reported for vinylogous thiol esters and α-oxo ketene dithioacetals that do not fit into the above categories. The S atom(s) in these substrates can be oxidized with a variety of reagents. Oxidation of β-alkylthio-α,β-enones and enoates has been effected with *m*-chloroperbenzoic acid[156a,b] and with $NaIO_4$.[123,156a] These β-sulfinyl derivatives have been exploited in the Diels–Alder reaction (Eq. 124, Table 29) and as Michael substrates[123] with a variety of nucleophiles in a substitution reaction involving an addition–elimination sequence (Eq. 127). Oxidation of α-oxo ketene dithioacetals with *m*-CPBA affords a variety of oxidation products depending upon the number of equivalents of reagent employed (Eq. 128).[17b] The mono-sulfoxide, bis-sulfoxide, and epoxy bis-sulfone were obtained with 1, 2, and 5 equivalents of reagent, respectively. Utilization of 3–4 equivalents of *m*-CPBA gave mixtures of products and the bis-sulfone was never obtained under these reaction conditions. The ketene bis-sulfone was obtained with H_2O_2 in glacial acetic acid (Eq. 129).[52]

The photosensitized reaction of α-oxo ketene dithioacetals with singlet oxygen has been reported.[158] The reaction affords products arising from cleavage of a dioxatane when carried out in methanol



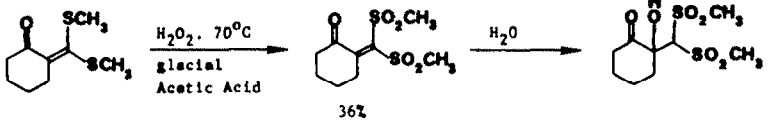
R	Nucleophile R^1-M(H)	% Yield
H	$NaCH(CO_2Et)_2$	78
	$NaCMe(CO_2Et)_2$	NR
	$NaCH(CN)CO_2Et$	89
	$NaCH(CO_2Et)COMe$	54
	$NaCH(CO_2Et)CH_2CH_2CH_2CH_3$	10
Me	$NaCH(CO_2Et)_2$	70
	Pyrrolidine	79.4
	NaOMe	94

eq. 127



Equivalents	% Yield	
1.0	65	
2		44
5		56
3-4	mixture	mixture

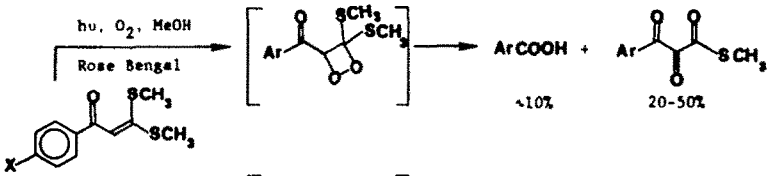
eq. 128



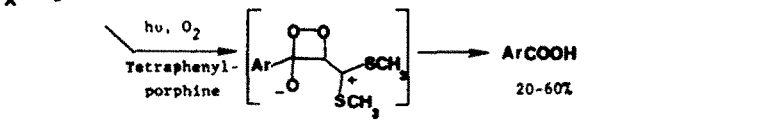
eq. 129

with rose bengal as sensitizer (Eq. 130). In benzene the reaction takes a different course with tetraphenylporphine as sensitizer and the products are believed to arise from a dioxatane generated by the addition of superoxide ion to the ketone carbonyl (Eq. 131). The superoxide ion is believed to be generated by electron transfer with the S atom as an electron donor.

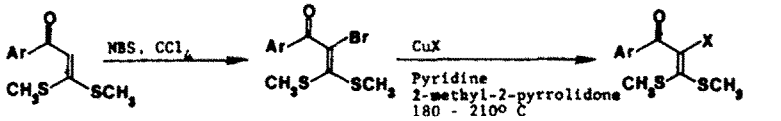
Electrophilic bromination of α-oxo ketene dithioacetals affords α-bromo-α,β-bis(alkylthio)-α,β-enones which undergo nucleophilic substitution with copper(I) cyanide or copper(I) arenethiolates (Eq. 132).[159] Copper(I) n-butanethiolate effected substitution of the Br atom and the β-methylthio group(s) by the n-butylthiolate nucleophile. The Br substituent could not be replaced with primary or secondary amines.



eq. 130



eq. 131



Ar	% Yield	X	% Yield
Ph	98	CN	78
		SPh	72
4-ClC_6H_4	98	CN	78
		SPh	66
4-MeC_6H_4	99	CN	71
		3-$CH_3C_6H_4S$	67
2-naphthyl	94	CN	68

eq. 132

8. SUMMARY

β-Alkylthio- and β,β-bis(alkylthio)-α,β-enones and enoates are highly functionalized α,β-unsaturated carbonyl substrates which can undergo a variety of transformations. Reactions can occur at the carbonyl, double bond, or S atoms, and deprotonation can occur at several sites depending upon substrate structure. The principal reactivity patterns involve 1,2-nucleophilic additions and 1,4-conjugate addition reactions to the enone or enoate functional group. The α-oxo ketene dithioacetals have proven, so far, to be the most versatile member of this group. The presence of two β-alkylthio substituents affords a higher level of oxidation in functional group manipulations and

in many instances generates a product containing an S substituent or functional group that can be manipulated in additional synthetic transformations. A variety of "one pot" transformations employing a cascade of 1,2- and 1,4-nucleophilic addition reactions to α-oxo ketene dithioacetals have been elegantly applied to a variety of heterocyclic syntheses. More recently, these two principle reactivity modes of α-oxo ketene dithioacetals have been separated in a controlled fashion and exploited for the sequential regio-, stereo-, and chemoselective construction of new C—C bonds. These synthetic methods should enhance the synthetic utility of the α-oxo ketene dithioacetal functionality as an extremely versatile three carbon synthon for functional group manipulations and C—C bond constructions.

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