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α-OXOKETENE-S,S-, N,S- AND N,N-ACETALS: VERSATILE INTERMEDIATES IN ORGANIC SYNTHESIS

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CONTENTS

1. INTRODUCTION

The polarised ketene dithioacetals[1] of the general formula **1**, which may carry either one or two electron withdrawing groups at the α-carbon atom (Table 1 and Chart 1) belong to a class of intermediates, generally known as either polarised,[2a,b] push–pull[2a,b] or donor–acceptor[2b] ethylenes. They are easily prepared by reacting the corresponding active methylene compounds with carbon

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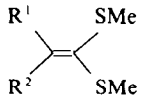
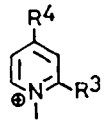
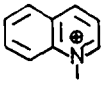
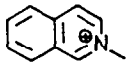
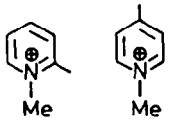
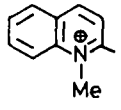
Table 1. Acyclic polarised ketene dithioacetals



1

R^1	R^2	References[a]
—CHO	H, Me, Et, Ph	3, 4
—COR^3		
R^3 = aryl, alkyl, cycloalkyl, 2-furyl, 2-thienyl, 2-, 3-pyridyl, styryl	H, alkyl, aryl, benzyl alkenyl, acyl, aroyl, CH_2CN, α-pyridyl	5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17
CN	H, aryl, 3-indolyl, α-pyridyl, aroyl, 2-thienoyl, 2-furoyl, CN	8*a*, 18, 19, 20, 21, 22, 23, 24, 25, 26
CO_2Et, CO_2Me, CO_2H	H, alkyl, benzyl, vinyl, aryl, MeCO, ArCO, CN, CO_2Me, CO_2Et, $CONH_2$	5*b*, 7, 20, 26, 27, 28, 29, 30, 31, 32, 33
$CONH_2$	CN	20, 26, 33
NO_2	H, PhCO, CO_2Et	1*d*, 2*b*, 34, 35, 36
R^1SO_2—	H, CN, COMe, Ar, CO_2Et	37, 38, 39, 40, 41, 42
R^1 = Ph, alkyl	Alkyl SO_2—, COPh	
		
$R^3 = R^4$ = H, Me	H, CN, Et, PhCO, CO_2Et, $CONH_2$	1*e*, 43, 44, 45, 46, 47, 48, 49, 50
		
	CO_2Et	50
	H	1*e*, 51, 52, 53
		

[a] References for methods of preparation.

disulphide in the presence of a suitable base followed by alkylation, often in a one-pot reactior Many experimental variations have been developed within this broad procedural framework to s the substrate characteristics such as the acidities of active methylene hydrogens, specific ba sensitive functional groups and the optimum yields of the corresponding dithioacetals. A la number of active methylene compounds could therefore be converted into the polarised kete dithioacetals with many permutations and combinations of substituents (Table 1 and Chart 1).

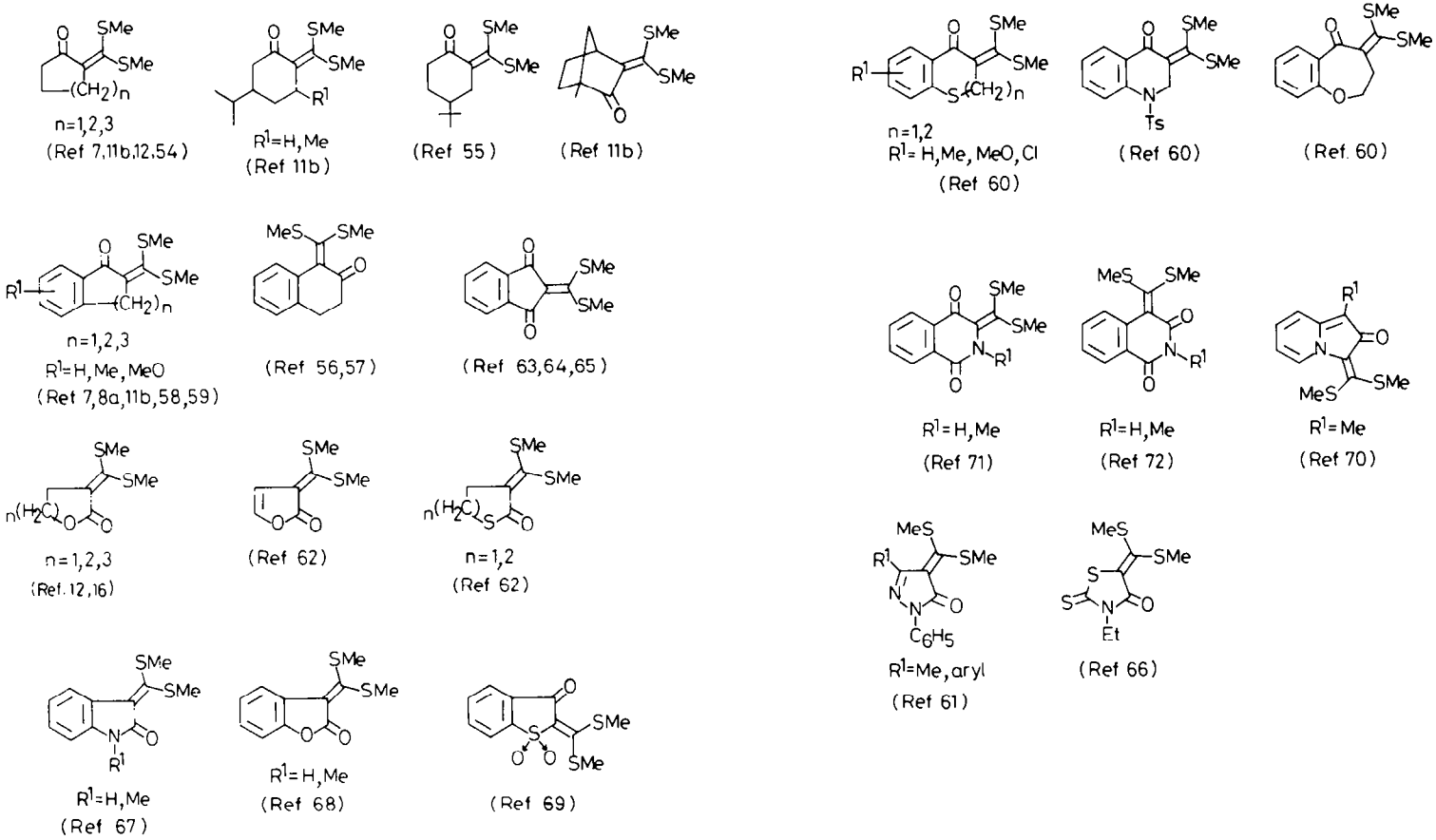


Chart 1. Cyclic and heterocyclic oxoketene dithioacetals.

The β-alkylthio groups in these intermediates are activated by the presence of polar substituents at the α-position and can therefore be displaced sequentially, either one or both, by various carbon, nitrogen and oxygen nucleophiles, creating further scope for introducing new functionalities at the β-position which find application in many synthetic transformations (Scheme 1).

The polarised ketene dithioacetals can be broadly classified into two categories:

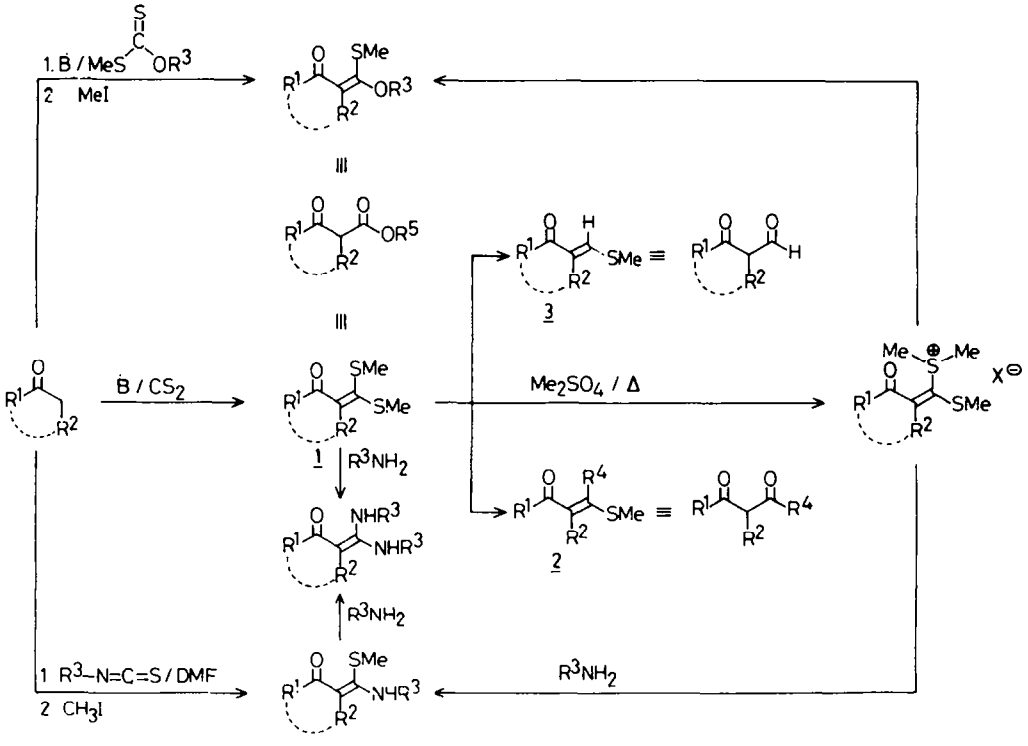
1. The ketene dithioacetals, which include all variants of oxo groups, such as CHO, CO, CO_2R, $CONH_2$ and the C≡N (as latent oxo group) can be considered as oxoketene dithioacetals (Table 1).

2. The other ketene dithioacetals that can be grouped separately include those which carry nitro, pyridinium and sulphonyl groups as α-polar substituents.

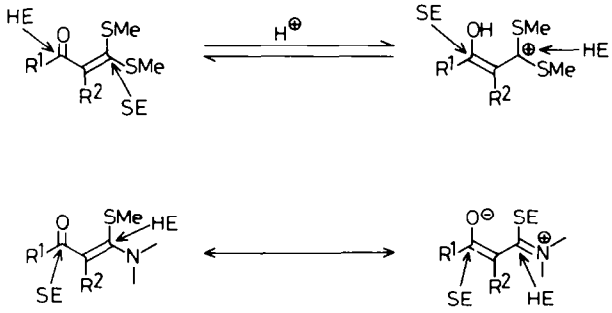
The first category may further vary in its α-substituents R^1 and R^2 of which R^1 has to be an oxo functionality, while R^2 could either be hydrogen or any other neutral group including those polar variants of the second category as described in Table 1.

Due to the limited scope and length of the present review, only the chemistry of α-oxoketene dithioacetals is covered and not that of the other polarised ketene dithioacetals, despite their many synthetic applications.[1d,1e]

The α-oxoketene dithioacetals owe their potential synthetic applications to their varied intrinsic chemical properties. The presence of carbonyl functionality and its position in conjugation with double-bond carrying bis(alkylthio) groups at the β-position places them among the versatile 1,3-electrophilic 3-carbon equivalents. The α-oxoketene dithioacetals can be considered as masked β-keteoesters that can be distinguished by having ambident electrophilicity at 1,3 carbon centres, due to the presence of bisalkylthio groups, which can be converted into ester functionality when desired.[7]



Scheme 1.



Scheme 2. Hard–soft affinity inversion in α-oxoketene S,S- and S,N-acetals. HE = hard electrophile, SE = soft electrophile.

Similarly, their immediate derivatives **2** and **3** can be considered as equivalents of β-diketones and β-ketoaldehydes respectively (Scheme 1). In addition, they can be further converted into enaminones and β-alkoxy-α,β-unsaturated ketones, making them highly functionalised master key intermediates, which could encompass the wide range of 1,3-electrophilic three-carbon fragments that are of great synthetic importance (Scheme 1).

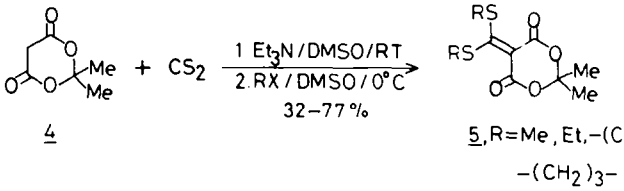
The carbonyl and the β-carbon atoms in these systems can also be regarded as hard and soft electrophilic centres, since the carbonyl is adjacent to the hard-base oxygen while the β-carbon is flanked by the soft-base thiomethyl groups (Scheme 2). Thus many regioselective reagents can be selected either from hard nucleophiles that can undergo 1,2-addition or from soft nucleophiles that can add preferentially in 1,4-fashion depending on the regiodemands in the product. Interestingly, this hard–soft disymmetry can be inverted[73] either under suitable reaction conditions or by structural modifications, by replacing a thiomethyl group with an amino group so that the same group of nucleophiles can be made to react with either of the carbon atoms to yield the respective regioisomers. Only a limited number of examples based on this concept can be recognised from this review, while the future possibilities remain largely unexplored. The flexible functional group manipulation, coupled with hard–soft disymmetry and its possible inversion, make these intermediates attractive for many synthetic schemes used to construct a variety of acyclic, cyclic and heterocyclic systems.

When we started work on oxoketene dithioacetals around 15 years ago, much of the chemistry of these compounds was confined to their preparation and properties, while their synthetic potential remained scantly explored. Over the years, many groups have made significant contributions to the chemistry of these compounds and a recent review by Dieter[1a] highlights the chronology of the development of their chemistry, structure and synthetic applications. The present review is complementary to Dieter's report and highlights only the developments made subsequently during this short span of time. The review is based on their chemical reactivity rather than product novelty, which may be appreciated by those who are interested in further exploration of the hidden synthetic potential of these intermediates. The latter half includes the synthetic applications of the corresponding N,S- and N,N-acetals.

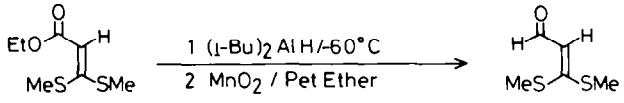
2. SYNTHESIS OF α-OXOKETENE DITHIOACETALS

The preparation and properties of α-oxoketene dithioacetals have been extensively reviewed by Dieter, and there have been no particular new advancements since then. The reaction of enolate anions derived from the active methylene carbonyl compounds in the presence of a suitable base/solvent combination (coupled with temperature manipulation) with carbon disulphide followed by alkylation, continues to be the preferred method for the preparation of these compounds.

The alkali sensitive Meldrums acid **4** has been converted into the corresponding bis-alkylthiolydine derivatives **5** in moderate to good yields by generating its enolate anion in the presence of triethylamine as base in dimethyl sulphoxide (eq. 1).[74] The formylketene dithioacetal **7** which could not previously be prepared directly from acetaldehyde enolate anion, has now been obtained in good yields from α-carbethoxy ketene dithioacetal **6** involving a reduction, oxidation sequence (eq. 2).[3]

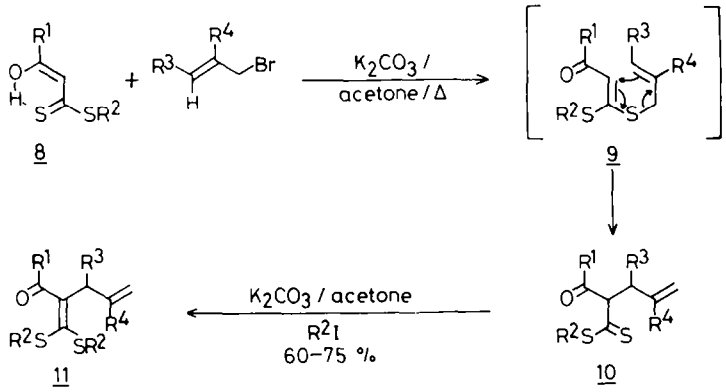


4 5, R=Me, Et, $-(CH_2)_2-$, $-(CH_2)_3-$ (1)



6 7 (2)

The difficulties encountered in the monoalkylation of ketene dithioalate salts to get the corresponding β-acyldithioesters was resolved by Lawesson and Larsson by using a counterion-pair technique.[75] Junjappa and Ila[76] developed subsequently an alternative facile method for the preparation of these dithioesters. Thus, enolate anions generated by sodium hydride in hydrocarbon solvent were reacted with dimethyl trithiocarbonate to give the corresponding dithioesters. The dithioesters are useful for the preparation of mixed dialkylketene dithioacetals which are particularly useful in the synthesis of thiophenes. The two step method of alkylation was advantageously extended to prepare the important group of α-oxo-α-alkenyl dithioacetals in moderate to good yields.[77] Thus the dithioesters **8** underwent spontaneous thio-Claisen rearrangement during alkylation with allyl, crotyl or methacrylyl halides to afford first the rearranged dithioesters **10**, which were further alkylated to afford the corresponding dithioacetals **11** (Scheme 3). The two step reaction



8 9 10 11

11, R^1 = Me, C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, R^2=Me, Et, $R^3=R^4=H$

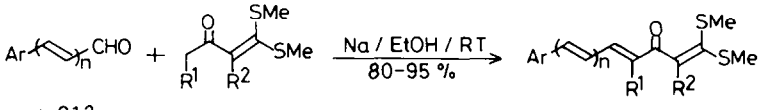
R^1 = Me, C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, R^2=Me, R^3=H, R^4=Me

R^1=4-ClC_6H_4, R^2=Me, R^3=Me, R^4=H

Scheme 3.

sequence was achieved in one pot through adding alkenyl and alkyl halides sequentially to afford **11** in identical yields.

Although the synthesis of cinnamoylketene dithioacetals and their higher enyl homologues can, in principle, be achieved from the corresponding enyl methyl ketones, no group appears to have examined these possibilities. However, Thuillier[5b] and subsequently Junjappa and Ila have reported the synthesis of these compounds by condensing the preconstructed acylketene dithioacetals with aromatic aldehydes, cinnamaldehydes and 5-aryl-penta-2,4-dienals in good yields (eq. 3). Apparently, the method could not be extended to aliphatic aldehydes for the preparation of the corresponding alkenoylketene dithioacetals. The problem was circumvented through the sequence of reactions given in eq. 4. Thus the acylketene dithioacetals **12** were converted to the enaminones **16** by treating **12** with dimethylformamide acetal in high yields. The enaminones **16** underwent clean 1,4-addition with alkyl magnesium halides to afford the corresponding alkenoylketene dithioacetal **17**.[78] Interestingly, though the 1,4-chemoselectivity towards hard nucleophiles in enaminones is not unusual, it can be best explained through hard–soft dissymmetry inversion (affinity inversion) by the presence of β-amino functionality in α,β-unsaturated ketones (eq. 4).

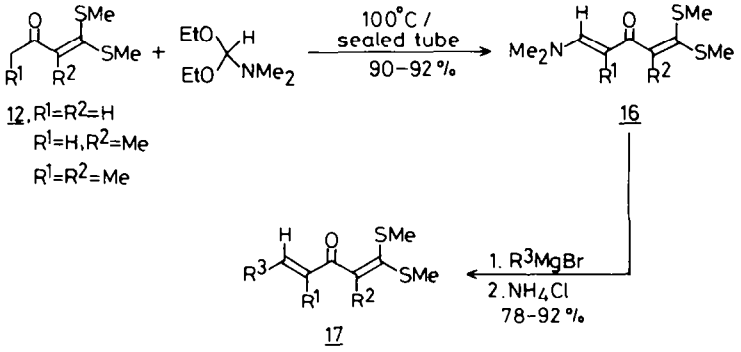


(3)

13, n=0, Ar=C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-MeOC_6H_4, 4-$NO_2C_6H_4$, 4-$Me_2NC_6H_4$, o-ClC_6H_4, m-MeOC_6H_4, 2,4-$Cl_2C_6H_3$, 2,6-$Cl_2C_6H_3$, 3,4-$(MeO)_2C_6H_3$, 3,4-methylenedioxyC_6H_3, 3,4,5-$(MeO)_3C_6H_2$; R^1=H, Me, R^2=H, Me, Et, n-Pr, i-Pr, n-Bu, n-heptyl, 90–95 %

14, n=1, Ar=C_6H_5, 4-MeC_6H_4, 4-MeOC_6H_4, 3,4-$(MeO)_2C_6H_3$, 3,4-methylenedioxyC_6H_3, 3,4,5-$(MeO)_3C_6H_2$, R^1= H, Me, R^2= H, Me, 80–85 %

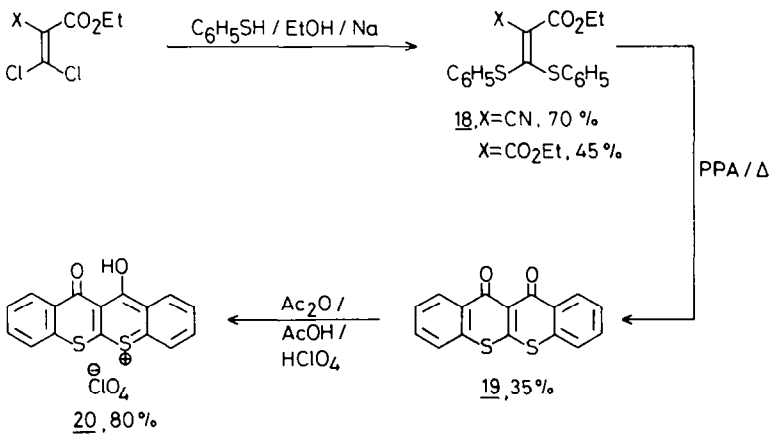
15 n=2, Ar=C_6H_5; 4-MeOC_6H_4, 3,4-methylenedioxyC_6H_3, R^1=H, Me, R^2=H, Me; 80–83 %



(4)

12, R^1=R^2=H
R^1=H, R^2=Me
R^1=R^2=Me

17, R^1= R^2= H, R^3= Me, Et, n-Pr, i-Pr
R^1=H; R^2=Me; R^3= Me, Et, n-Pr, i-Pr
R^1= R^2= Me, R^3= Me, Et, n-Pr, i-Pr



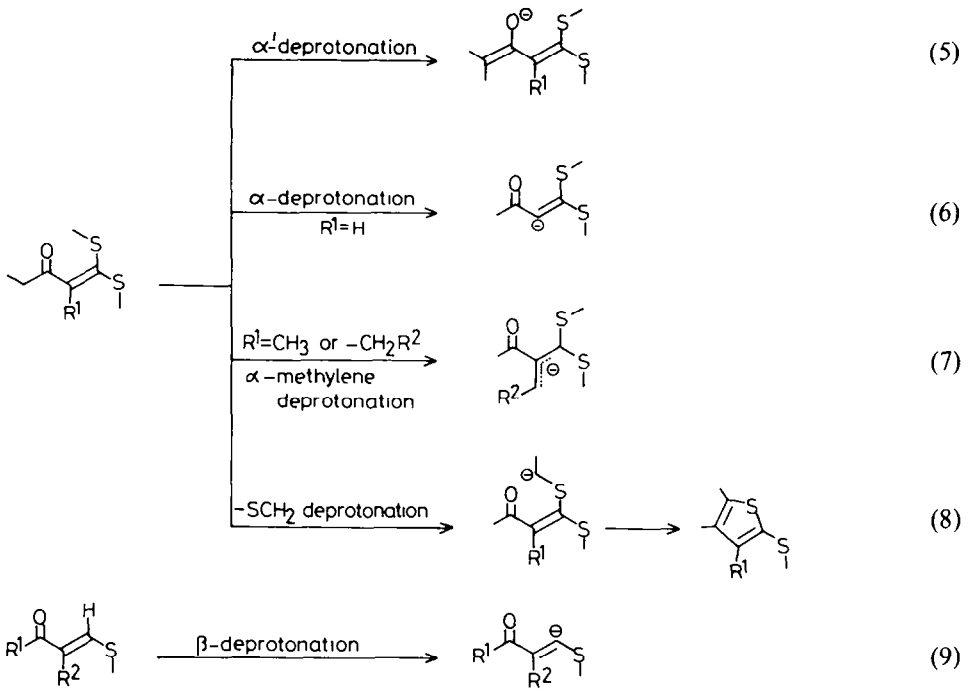
Scheme 4.

The bis(arylthio)derivatives **18**, which could not be prepared through the corresponding dithiolate anions, have been prepared by nucleophilic displacement of β-dichloro groups by arylthiolate anions in the corresponding enoates (Scheme 4).[79,80] These acetals **18** have been shown to undergo intramolecular cyclocondensation to yield the corresponding benzothiopyranobenzothiopyran **19** in moderate yields (Scheme 4). The β-oxodithioacids are shown to undergo nucleophilic substitution with 2,4-dinitrochlorobenzene to give [1,3-benzo-dithiol-2-ylidene] carbonyl compounds.[81] Similarly, nucleophilic displacement and cyclocondensation of dithioacids with haloketones afford 1,3-dithiolydene ketones in good yields.[82] Alternatively, the corresponding 1,3-benzodithiolydene ketones have been recently prepared by the reaction of active methylene ketones with 1,3-benzodithiolium tetrafluoborate.[83] However, these 1,3-dithiolydene ketones[84] do not fall under the purview of this report and have not been covered.

3. DEPROTONATION

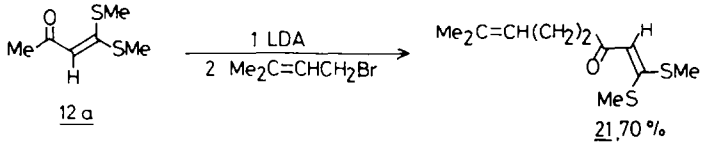
The oxoketene dithioacetals undergo deprotonation in various ways depending on their structural characteristics and the reaction conditions employed. These studies have resulted in the development of many synthetically useful transformations and interesting rearrangements.

The acylketene dithioacetals undergo facile α'-deprotonation to afford the corresponding enolate anions (eq. 5), while α-deprotonation is observed when the acyl group is replaced by a benzoyl group to give the corresponding vinyl carbanion (eq. 6). Similarly in the α-alkylbenzoylketene dithioacetals, the methyl/methylene protons are deprotonated to yield the corresponding 2-oxoallyl anions as shown in eq. 7. The thiomethyl protons in aroyl ketene dithioacetals can also be abstracted under appropriate conditions and the resulting carbanion is found to undergo intramolecular aldol condensation to yield the corresponding thiophenes (eq. 8). This approach is an extension of the earlier thiophene synthesis from activated thiomethyl groups by replacement of one of the methyl hydrogens with electron withdrawing groups using mild basic conditions. The β-deprotonation of vinylogous thiolesters affords vinyl carbanions (eq. 9) which are found useful in cyclopentanone annelation[85,86] and in the synthesis of mixed oxoketene dithioacetals containing different alkylthio groups.[87]

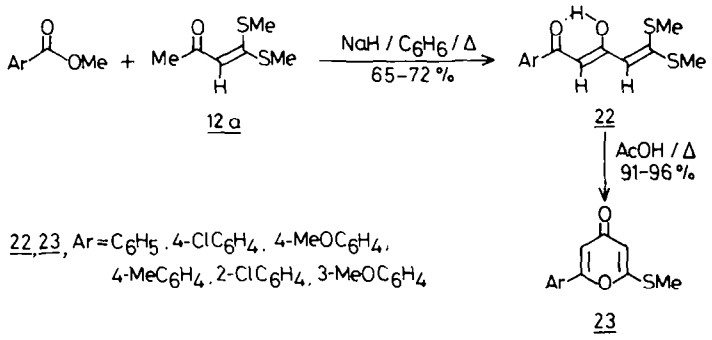


3.1. *α'-Deprotonation*

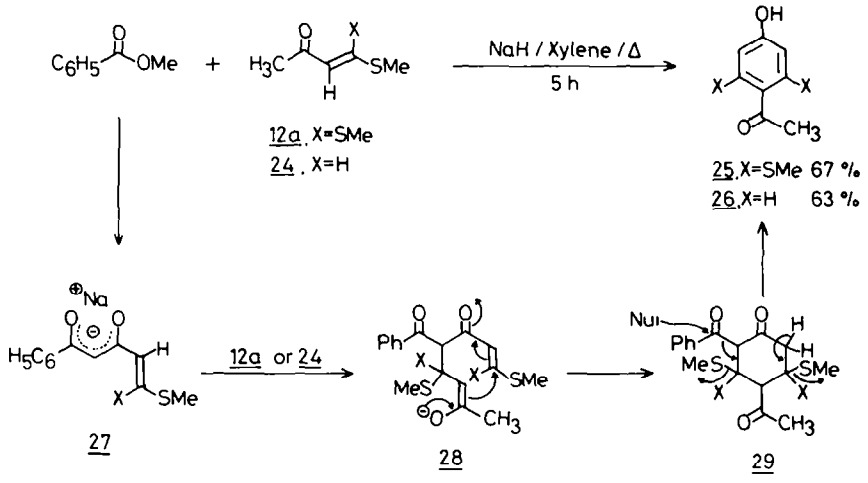
Base catalyzed aldol condensation of acylketene dithioacetals **12** with aromatic and α,β-unsaturated aldehydes and their higher homologues to give the corresponding enoylketene dithioacetals has been discussed earlier (eq. 3). These enolate anions have been alkylated to yield the higher homologues of ketene dithioacetals in varying yields. Thus the dithioacetal **21**, an intermediate required for the synthesis of perillene[88] was obtained in good yield by alkylation of **12a** with prenyl chloride in the presence of LDA (eq. 10). Similarly the enolate anion of **12a** was condensed with



the methyl benzoates to give the corresponding β-diketones **22**, which were subsequently cyclised in the presence of acetic acid to afford the corresponding 2-aryl-6-methylthio-4H-pyran-4-ones **23** in high yields[89] (Scheme 5). However, when **12a** was reacted with methyl benzoates in refluxing xylene under identical conditions, the corresponding 2,6-bis(methylthio)-4-hydroxyacetophenones **25** were formed in good yield[89] (Scheme 6). Similarly the β-methylthioenone **24** gave the corresponding 4-hydroxyacetophenone (**26**) under identical conditions. A possible mechanism for the formation of **25** and **26** could involve base catalysed self condensation of either **12a** or **24** through successive inter- and intramolecular Michael additions followed by elimination of the methylmercapto group.[89] However, these transformations occur only in the presence of methyl benzoate, which appears to involve the formation of enolate anion **27** and subsequent addition and elimination to afford **25** or



Scheme 5.

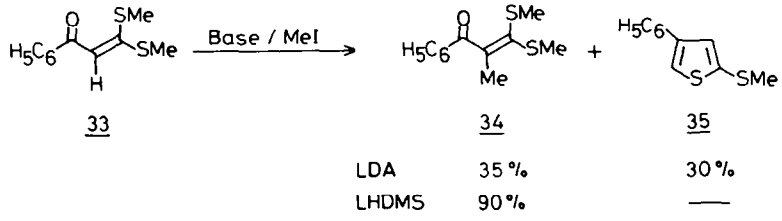


Scheme 6.

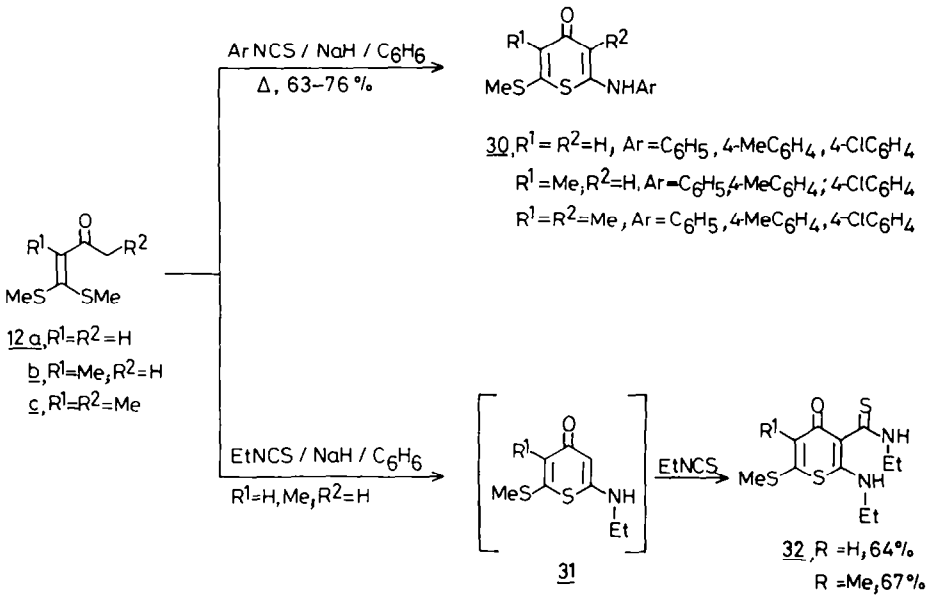
26 (Scheme 6). The acyl enolate anions also undergo addition to arylisothiocyanates followed by intramolecular ring closure to give 6-arylamino-2-methylthio-4H-thiopyran-4-ones **30** (Scheme 7).[90] The intermediate 6-ethylaminopyrone **31**, formed under identical conditions with ethyl isothiocyanate, underwent further addition with a second mole of ethyl isothiocyanate to yield **32** (Scheme 7).[90]

3.2. *α-Deprotonation*

Marino and co-workers[91] α-deprotonated **33** in the presence of LHDMS and alkylated the anion using methyl iodide to afford the corresponding α-methyl oxoketene dithioacetal **34** in high yield. However, competitive deprotonation of thiomethyl protons occurred when LDA was used as a base to yield a mixture of thiophene **35** (30%) and the alkylated product **34** (35%) (eq. 11).



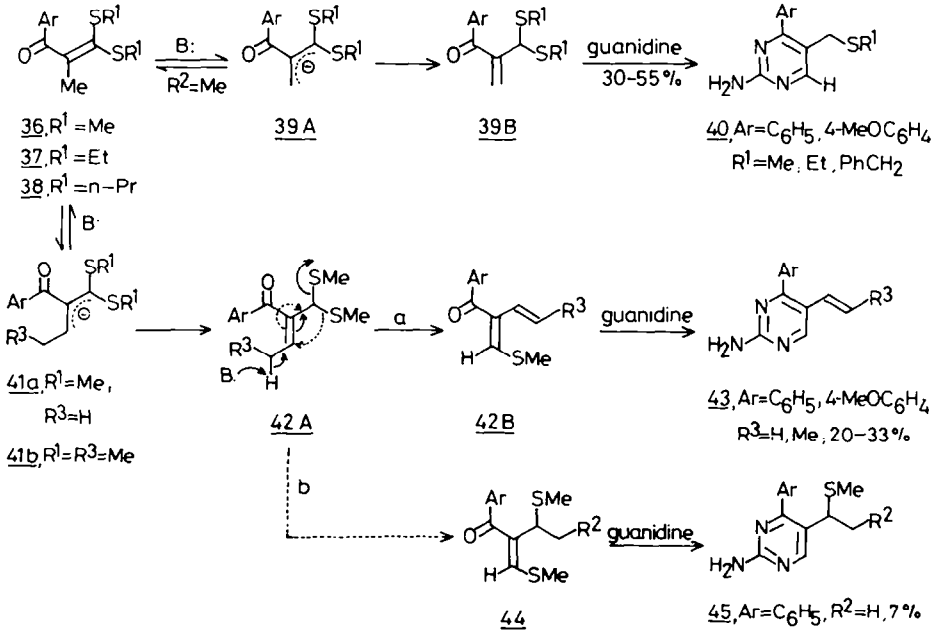
(11)



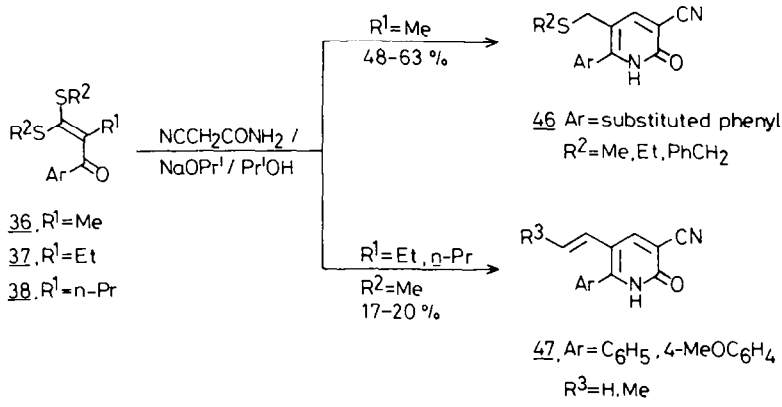
Scheme 7.

3.3. α-*Methyl/methylene deprotonation*

In their earlier report, Chauhan and Junjappa[8b] had observed that the α-methyl oxoketene dithioacetal **36** could condense with guanidine in the presence of sodium alkoxide to give 5-alkylthiomethylpyrimidines **40** in moderate to good yields (Scheme 8). The formation of **40** was



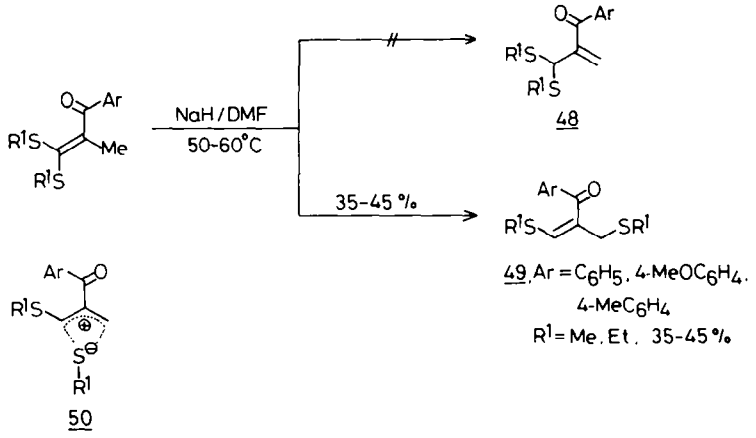
Scheme 8.



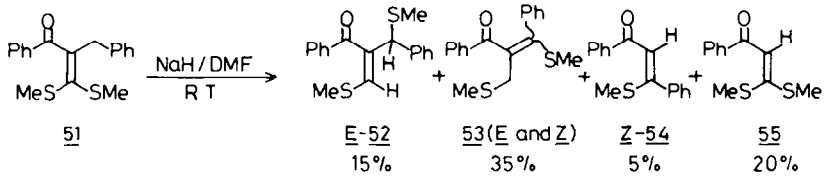
Scheme 9.

explained through intermediate **39B** involving deprotonation of the α-methyl proton of **36** and subsequent isomerisation. The corresponding α-ethyl (**37**) and α-(*n*-propyl) (**38**) oxoketene dithioacetals underwent similar deprotonation followed by elimination of the methylmercapto group to give the intermediate **42B** (Scheme 8)[8h] which on subsequent reaction with guanidine afforded the pyrimidines **43**. The formation of the pyrimidine **45** in low yield was postulated through **44** involving a 1,3-MeS shift (Scheme 8). The reaction of cyanoacetamide with α-alkyl oxoketene dithioacetals under basic conditions to form the rearranged pyridones **46** and **47** were also similarly explained (Scheme 9).[92]

Attempts to isolate the mobile ketoallyl intermediates **48** by α-methyl deprotonation of **36** in the presence of sodium hydride led to the isolation of 2-methylthiomethyl-3-methylthioacrylophenones **49** apparently involving a 1,3-alkylthio shift (Scheme 10).[93] Junjappa and Ila have proposed an intermolecular 1,3-alkylthio shift for these transformations and extended these rearrangement studies to α-benzyl **51**[9] and cyclic α-methylene oxoketene dithioacetals[59] to afford similarly rearranged products and the products thereof (eq. 12). The concerted 1,3 sigmatropic shift or a sulphur assisted



Scheme 10.



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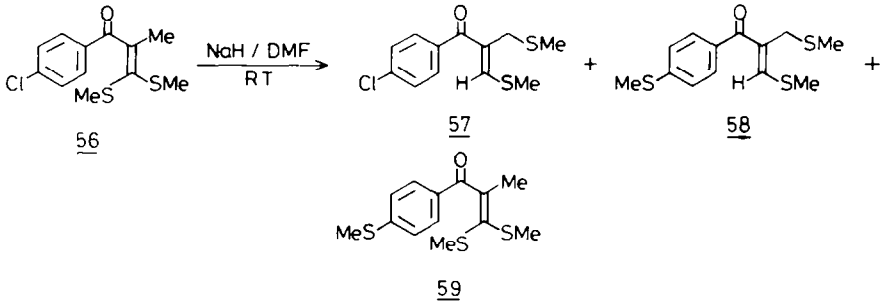
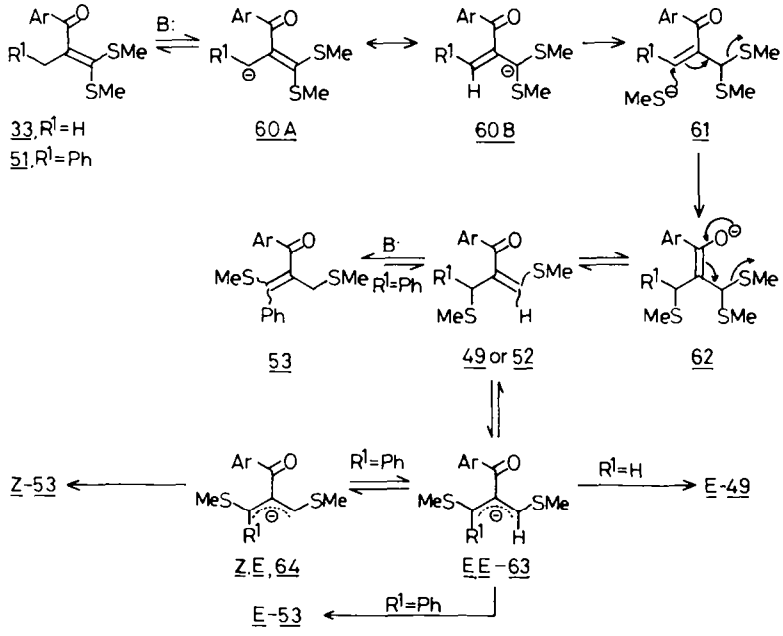


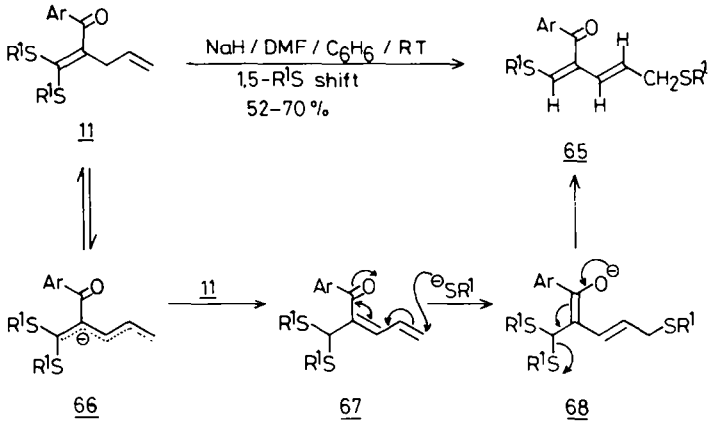
(13)

polar concerted mechanism through transient complex **50** to form **49** or **53** was ruled out by experiments and an alternative intermolecular thioallylic rearrangement was established. Thus, in addition to the expected product **57** from *p*-chloroderivative **56**, the formation of other products **58** and **59** confirmed the intermolecularity of the rearrangement (eq. 13). The proposed mechanism involves Michael addition of thiolate anion to **61** to yield solvent equilibriated enolate anion **62** followed by elimination of methylthio group (Scheme 11).[9]

Alternatively, the α-allyl oxoketene dithioacetals **11** were considered suitable for concerted 1,5-alkylthio shift under identical reaction conditions. On treatment of **11** with sodium hydride and

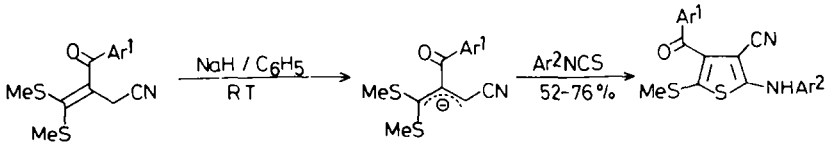


Scheme 11.



Scheme 12.

DMF, the expected dienes **65** were formed in good yields (Scheme 12).[77] However, the 1,5-alkylthio shift in **11** was also proved to be intermolecular migration rather than concerted, involving 1,6-conjugate addition to mobile oxopentadienyl intermediate **67** derived from anion **66** under reversible conditions (Scheme 12).[77] In their subsequent studies Junjappa and Ila were able to trap the stable 3-cyanopropenide anion **70** (eq. 14, 15) by reacting them with activated heteromultiple bonds in an effort to obtain anionic [3+2] cycloadducts.[94] Thus **70** underwent cyclocondensation with aryl isothiocyanates to yield substituted thiophenes **71** presumably through initial stepwise or concerted anionic [3+2] cycloaddition to a C=S bond.[94] On the other hand the addition of **70** to *p*-chlorobenzaldehyde carbonyl double bond gave the diastereomeric ketal **72** which, on treatment with $BF_3 \cdot Et_2O$/MeOH, afforded the corresponding methyl ketal **73** and the furan **74** in 55% and 40% yields, respectively.[94] Attempted cycloaddition of **70** to benzonitrile (C≡N) gave only the dimeric product **75** (eq. 16) formed by self condensation of **69** and the reaction proceeded only in the



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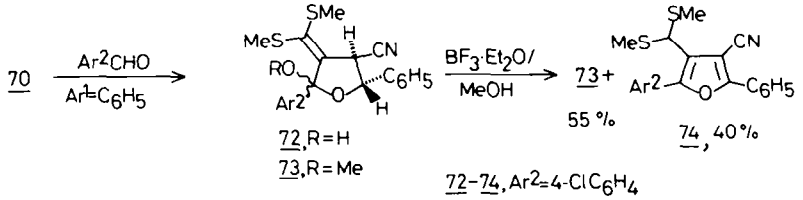

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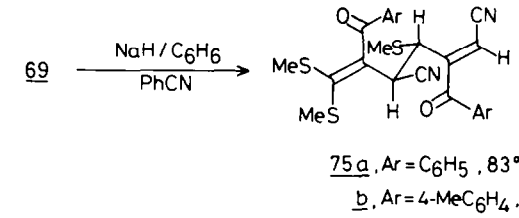
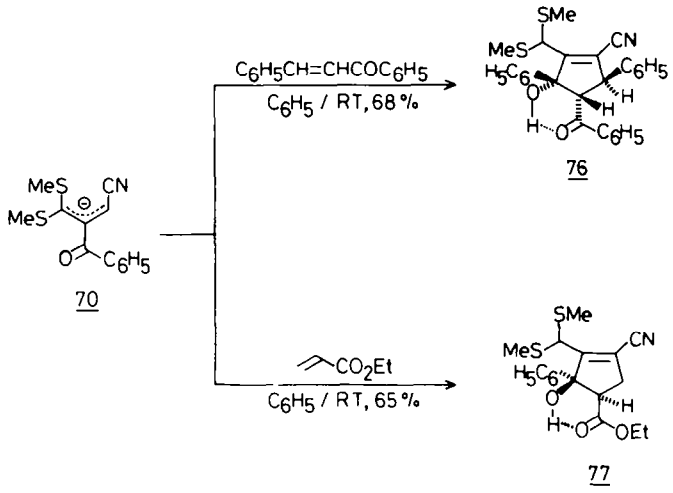


(16)

75 a, Ar = C_6H_5, 83%
b, Ar = 4-MeC_6H_4, 76%

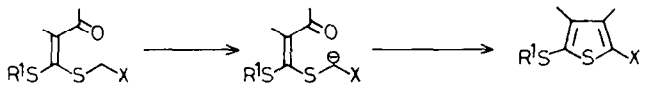


Scheme 13.

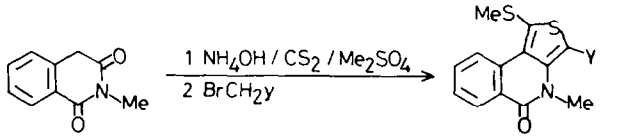
presence of benzonitrile.[94] Similarly, the cyclocondensation of **70** either with chalcone or with ethyl acrylate gave the cyclic alcohols **76** and **77** respectively (Scheme 13).[95] Interestingly, these cyclisations were found to be highly diastereoselective and only one stereoisomer was isolated from the reaction mixture. The coordination of enolate and carbonyl oxygen atom with metal ion during cyclisation appears to be responsible for the observed diastereoselectivity. The adduct **76** was found to be resistant to acetylation and dehydration probably due to intramolecular hydrogen bonding[95] and its structure and stereochemistry was confirmed by X-ray crystallography.

3.4. *Deprotonation of thiomethyl/methylene group*

The facile deprotonation of oxoketene dithioacetals carrying acidic thiomethylene groups (X = CN, CO_2Et, COR) and subsequent intramolecular aldol condensation of the carbanions to give substituted thiophenes (eq. 17) was reported earlier by several workers.[34,75a] These reactions occur invariably *in situ* during alkylation of dithioic acids with α-halonitriles, esters or ketones. Subsequently the reaction was developed as a general method for thiophene synthesis by sequential alkylation of dithioic acids[16a,23,58] with methyliodide and activated alkyl halides to yield mixed ketene dithioacetals, so that the carbanion generated under mild basic conditions could undergo intramolecular aldol condensation to yield the corresponding thiophenes (eq. 17; R^1=Me, X=CN, CO_2Et, CO_2R).[96] Subsequently, Marino[91] and co-workers deprotonated thiomethyl protons of oxoketene dithioacetals using LDA and the resulting carbanion underwent cyclisation to afford 3,4-disubstituted thiophenes. However, the corresponding bis(ethylthio) ketene dithioacetals (R^1=Et, X=Me) could not undergo deprotonation under these conditions.[91] The scope and limitations for

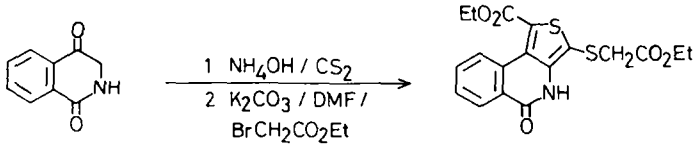


(17)



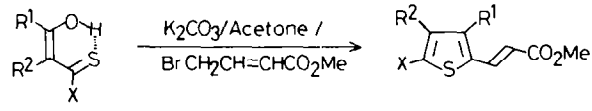
78 79 Y=CN, 40%; Y=CO_2Et, 60%

(18)



80 81

(19)



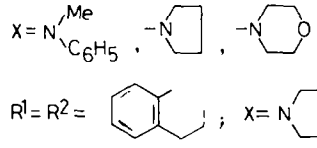
8, X=SMe, Et
82, X=amino

83, X=SMe, SEt
84, X=amino

(20)

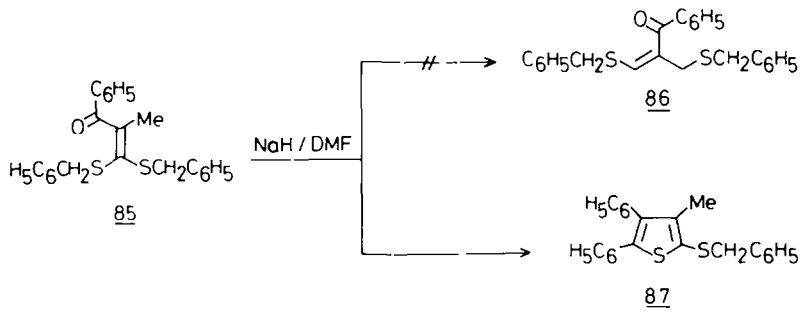
83, R^1=Me, C_6H_5, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 2-thienyl, 2-furyl; R^2=H, Me; X= SMe, SEt; 73-88%

84, R^1=C_6H_5, 4-ClC_6H_4, Me, 2-furyl; R^2=H, Me



65-82%

these transformations have been covered in detail by Dieter in the earlier review. Kobayashi and co-workers have reported the synthesis of thienoisoquinoline derivatives **79** and **81**[71,72] (eq. 18 and 19) using this methodology. Junjappa and Ila, during their studies on thio-Claisen rearrangement observed that the reaction of dithioesters **8** with bromocrotonate in the presence of K_2CO_3 afforded the corresponding thiophene acrylates **83** rather than the rearranged products.[97] Under identical conditions the *β*-oxothioamides **82** yielded the corresponding 5-aminothiophene-2-acrylates **84** in good yields (eq. 20).[97] The α-methyl bis(benzylthio) oxoketene dithioacetal **85** yielded the thiophene **87** instead of the rearranged **86** suggesting that the relative acidities of the protons present in the oxoketene dithioacetals is a determining factor (Scheme 14).

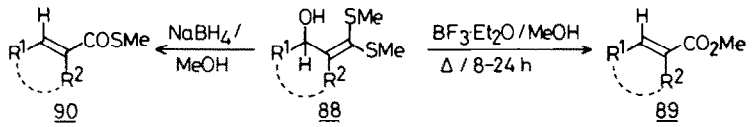


Scheme 14.

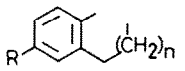
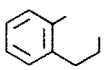
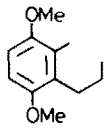
4. REDUCTION REACTIONS AND 1,3-CARBONYL TRANSPOSITIONS

The oxoketene dithioacetals and β-alkylthioenones possessing ambident electrophilic centre an α,β-enone moiety with either one or two β-alkylthio groups follow different pathways of reduct depending on the nature of the reducing agents. Ireland and Marshall[98] were the first to recog the importance of the β-alkylthio group during sodium borohydride reduction of α-(n-bu thiomethylene)ketones affording allylalcohols through chemoselective 1,2-reduction in high yie in contrast to the 20% 1,4-reduction product obtained as a mixture, when the correspon alkoxymethylene ketones were reduced by sodium borohydride. Evidently, the β-alkylthio gr was responsible for further rendering the β-electrophilic carbon softer thus facilitating the exclu chemoselective 1,2-reduction in these systems. These studies subsequently led to an extensive inv gation on chemoselective 1,2-reduction of α-oxoketene dithioacetals by $NaBH_4$ first by Saquet Thuillier,[99] who observed the formation of the corresponding allylic alcohols in high yields. T further studied the acid catalysed rearrangement of these carbinolacetals to afford a mixtur products of which α,β-unsaturated thiolesters were the major products. Reinvestigation of the a catalysed rearrangement of carbinolacetals was subsequently carried out by Dieter[100] and workers who developed an efficient combination of $HgO/Hg(OAc)_2$ with HBF_4 to yield either unsaturated thiolesters or the corresponding carboxylic acids depending on the stoichiometry of Hg salts. Similarly Junjappa and Ila[101] discovered that the carbinolacetals **88** could be efficie converted into α,β-unsaturated thiolesters ($BF_3 \cdot Et_2O/H_2O$) **90** or to the corresponding O-me esters **89** in the presence of $BF_3 \cdot Et_2O$/methanol (eq. 21). The overall transformation can viewed as the homologation of active methylene ketones at the α-position, involving 1,3-carbo transposition. The formation of α,β-unsaturated methyl esters constitutes a new general method the synthesis of cinnamates and α-substituted cinnamates with *E* geometry from the correspon acetophenones and higher homologues of acetophenones respectively. The substituted croton could also be obtained similarly from the respective alkylmethyl ketones in good yields (eq. Also, Nishio and Omote investigated the $NaBH_4/LiAlH_4$ reduction of β-alkylthio α,β-enones while Gammill *et al.*[103] showed that the $LiAlH_4$ reduction afforded diastereomerically pure *th* β-alkyl-γ-bis(methylthio)alcohols in high yields through 1,2 reduction followed by 1,4 reduction intramolecular hydroalumination. These studies have been discussed extensively by Dieter in review. Only electrophilic reducing agents such as DIBAL, 9-BBN and catechol-borane[104] co reduce the α-oxoketone dithioacetals in 1,4-fashion, which are covered by Dieter.

Among other reduction studies with $NaBH_4$ in combination with transition metal halides, c the method of Junjappa and Ila employing the $NaBH_4/NiCl_2$ (nickel boride) combination coul used effectively for the selective dethiomethylation of α-oxoketene dithioacetals to yield vinylog thiolesters in moderate to good yields.[105] A few of these vinylogous thiolesters derived fr

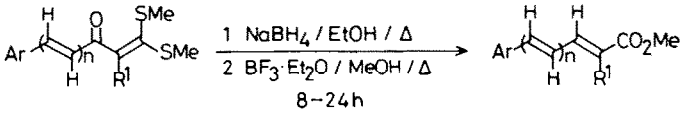


90 88 89 (21)

R¹	R²	% yield 90	R¹	R²	% yield 89	R¹	R²	% yield 89
C_6H_5	H	55	C_6H_5	H	70	$-(CH_2)_3-$		70
4-ClC_6H_4	H	60	4-ClC_6H_4	H	68	$-(CH_2)_4-$		75
4-$EtOC_6H_4$	H	75	4-$EtOC_6H_4$	H	72			
4-MeC_6H_4	H	75	C_6H_5	Me	67			
$-(CH_2)_3-$		55	C_6H_5	Et	75			
$-(CH_2)_4-$		70	C_6H_5	n-Pr	75	R=H; n=1		73
		65	Me	H	50	R=MeO; n=1		67
			Me	Me	54	R=H; n=2		70
			Me	n-Bu	74			80
			Me	n-C_5H_{11}	80			

methylalkylketones serve as important precursors in the synthesis of polyene with a terminal aldehyde group, which can be derived from β-methylthiomethylene functionality under hydrolytic conditions.[106]

The 1,2-reduction and methanolysis methodology was further extended to polyene ester synthesis (eq. 22). Thus cinnamolylketene dithioacetals **13a** underwent 1,2-reduction with sodium borohydride and subsequent methanolysis to give 5-aryl-pentadienoates in moderate to good yields,[107] while the corresponding 5-aryl-pentadienoylketene dithioacetals **13b** afforded the 7-aryl-2,4,6-heptatrienoates **92** (eq. 22).[108]



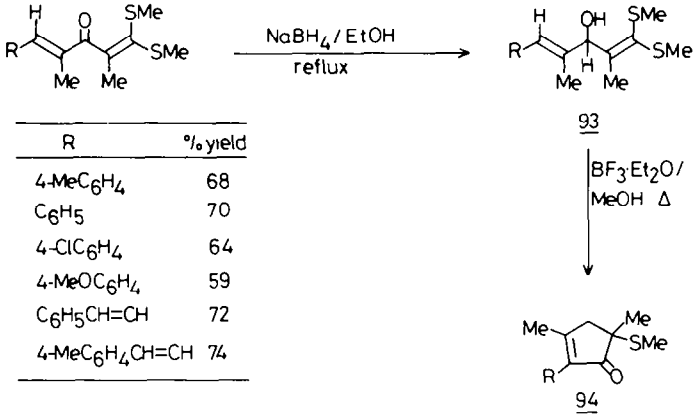
13 a, n=1
b, n=2

91, n=1
92, n=2 (22)

91, Ar = C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-ClC_6H_4, 3,4-methylenedioxyC_6H_3; R^1 = H, Me, n=1; 55–78%

92, Ar = C_6H_5, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3,4-methylenedioxyC_6H_3; R^1 = H, Me, n=2; 58–74%

The carbinol acetals formed by the reduction of 2,4-dimethylcinnamoylketene dithioacetals did not follow the observed pathway of methanolysis to afford the corresponding dieneesters and the products were characterised as the rearranged cyclopentenones **94** (Scheme 15).[109] Similarly, direct methanolysis of 2,4-dimethyl-cinnamoylketene dithioacetals in the presence of $BF_3 \cdot Et_2O/HgCl_2$ gave only the cyclopentenones **314** (Scheme 57) instead of the expected γ,δ-unsaturated β-ketoesters.



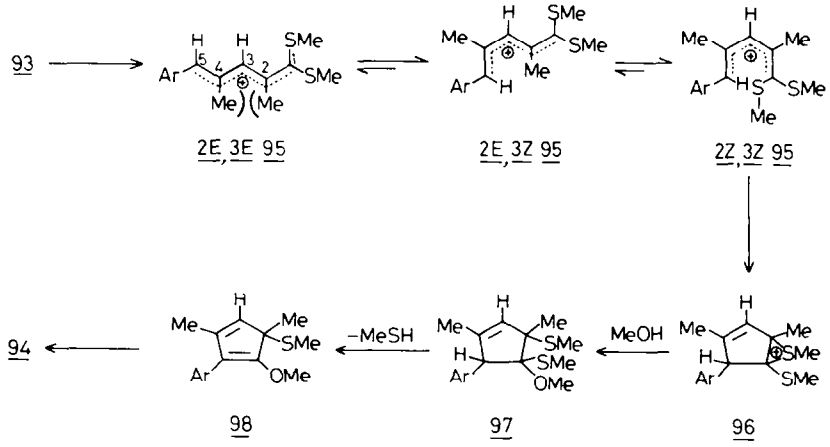
R	% yield
4-MeC$_6$H$_4$	68
C$_6$H$_5$	70
4-ClC$_6$H$_4$	64
4-MeOC$_6$H$_4$	59
C$_6$H$_5$CH=CH	72
4-MeC$_6$H$_4$CH=CH	74

93

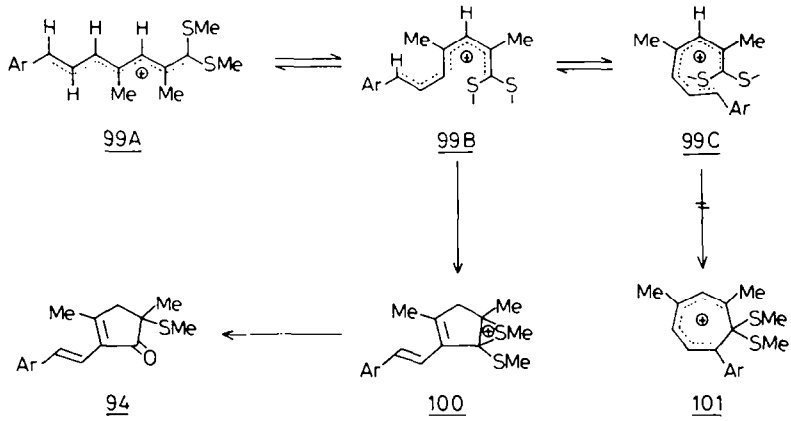
94

Scheme 15.

The mechanism governing the formation of these cyclopentenones can be rationalised through electrocyclic ring closure of the intermediate pentadienyl cations **95** (Scheme 16) and **315** (Scheme 57) both having the 4π electron system. The additional 2,4-methyl groups force the initially formed carbonium ions from a zig-zag conformation (having non-bonded steric repulsion between 2,4-methyl groups) to a twisted non-planar U conformation, thus creating favourable geometry for symmetry-allowed conrotatory thermal electrocyclic ring closure[110a] to afford the corresponding cyclopentenyl cations **96** (Scheme 16) and **316** (Scheme 57) respectively. The cyclopentenyl cation **96** is further stabilised by the adjacent methylthiogroup forming episulphonium ion, which undergoes methanolysis with concurrent MeSH shift to afford the intermediate O,S acetal **97**. Under acidic conditions, the labile cyclopentadiene ether **98** formed by elimination of methylmercaptan would finally cleave to afford the corresponding cyclopentenones **94** (Scheme 16). However, the hydroxycyclopentenyl cations **316** appear to undergo methanolysis followed by MeSH elimination to afford the corresponding cyclopentenones **314** (Scheme 57). Thus the conversion of 2,4-



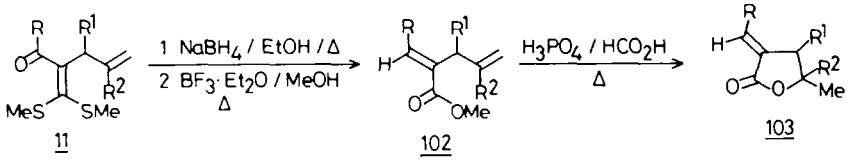
Scheme 16.



Scheme 17.

dimethylcinnamoylketene dithioacetals to cyclopentenones **314** (Scheme 57) can be viewed as Nazarov-type ring closure[110b] in the Lewis acid medium, while the formation of other cyclopentenones **94** (Scheme 15) from pentadienyl cation constitutes an unprecedented Nazarov-type ring closure where the masked ketene carbonyl group reappears from the mercapto functionality during work-up as depicted in Scheme 16. Under similar reaction conditions, the heptatrienyl cation **99**, a 6π electron system, could undergo cyclisation either through a folded non-planar conformation **99c** or through U subunit of zig-zag conformation **99B** to afford either cycloheptatrienyl cation or cyclopentenyl cation **100** respectively (Scheme 17). Only the styrylcyclopentenones **94** were formed, since 1,5 ring closure appears sterically the most favourable and higher polyenylic cation can always be written with U subunit conformer **99B** from a trienylic cation.[110c]

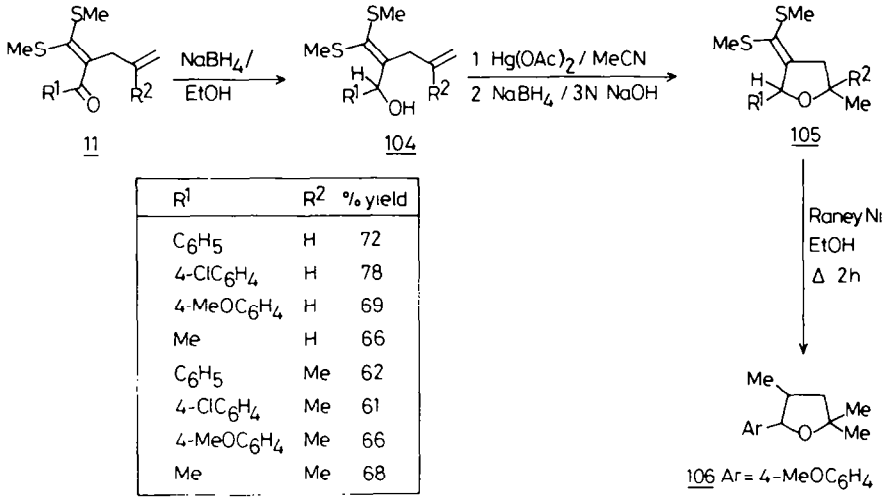
Junjappa and Ila have further extended these 1,2 $NaBH_4$ reduction studies to α-oxo-α-alkenyl ketene dithioacetals **11** and subjected the resulting enolacetals to methanolysis to afford the corresponding α-ylidene-γ,δ-unsaturated esters **102** in good yields (eq. 23). Subsequent hydrolysis and



(23)

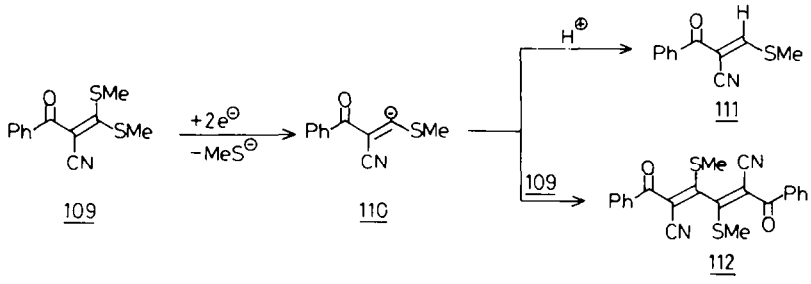
R	R^1	R^2	% yield 103	R	R^1	R^2	% yield 103
C_6H_5	H	H	98	C_6H_5	H	Me	76
4-ClC_6H_4	H	H	90	4-ClC_6H_4	H	Me	80
4-$MeOC_6H_4$	H	H	82	4-$MeOC_6H_4$	H	Me	75
4-MeC_6H_4	H	H	80	Me	H	Me	74
Me	H	H	80	4-ClC_6H_4	Me	H	70

enelactonisation of **102** in the presence of a 1 : 1 mixture of phosphoric and formic acid afforded the corresponding α-ylidene-γ-butyrolactones **103** in highly stereoselective manner (eq. 23).[111] Alternatively, the corresponding carbinols **104** were subjected to an oxymercuration/reduction sequence to afford the diastereomeric 2,5-substituted-3-bis(methylthio)methylenetetrahydrofurans **105** predominantly as *trans*-isomers (Scheme 18).[112] One of the furans (R^1 = 4-$MeOC_6H_4$; R^2 = Me) was



R^1	R^2	% yield
C_6H_5	H	72
4-ClC_6H_4	H	78
4-$MeOC_6H_4$	H	69
Me	H	66
C_6H_5	Me	62
4-ClC_6H_4	Me	61
4-$MeOC_6H_4$	Me	66
Me	Me	68

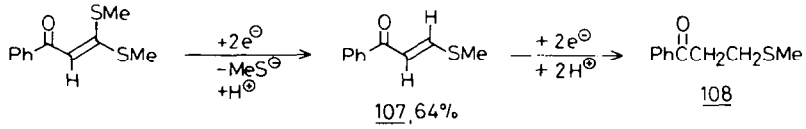
Scheme 18.



Scheme 19.

subjected to reductive desulphurisation in the presence of Raney-Ni to afford the corresponding 3,5,5-trimethylfuran **106** in good yields (Scheme 18). The highly chemoselective mercuration in these reactions which occurs without affecting the bis(methylthio) methylene functionality is noteworthy. These results are in conformity with earlier studies of preferential oxymercuration of terminal mono- or disubstituted olefins over the corresponding tetrasubstituted derivatives.[112]

In addition to chemoselective dethiomethylation of oxoketene dithioacetals by the $NaBH_4/NiCl_2$ combination to the corresponding β-alkylthioenones, Matschiner and Rudorf[113] have studied the cathodic reduction of oxoketene dithioacetals in protic media, which proceeds by cleavage of the S-alkyl group. The resulting carbanion **110** may either be protonated to give β-methylthio α,β-enones or react with unreacted dithioacetals to give dimeric products (eq. 24, 25, 26, Scheme 19). In subsequent studies Steckhan *et al.*[114] have shown that the cathodic reduction of cyclic oxoketene dithioacetals in the presence of tetrabutylammonium hydrogen sulfate affords the corresponding β-methylthio-α,β-enones **114** or **116** in high yields in thermodynamically favoured *E* geometries (eq. 25 and 26). Interestingly the cathodic cleavage of methylthio group in **115** occurs even in the presence of acetic anhydride, which acts as protonating agent at Hg cathode, which was experimentally proved by using hexadeuteroacetic anhydride as protonating agent.



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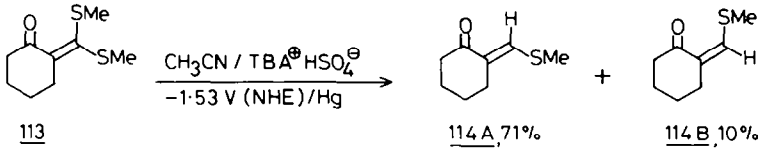
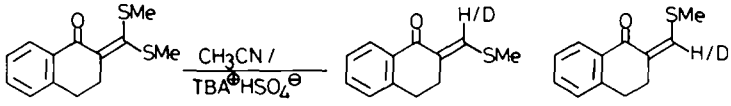


113 114 A, 71% + 114 B, 10% (25)

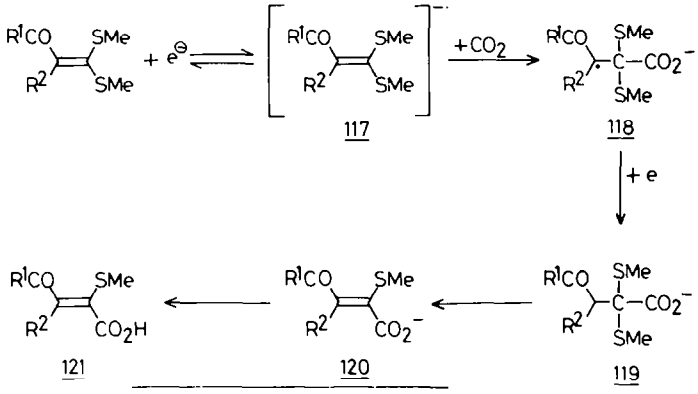


(26)

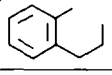
115

	116 A	116 B
−1·03 V(NHE)/Hg	69%	25%
−1·23 V(NHE)/Hg	60%	20%
$CH_3CN/(CH_3CO)_2O$/ −1·43 V(NHE)/Hg	54%	8%
$CH_3CN/(CD_3CO)_2O$/ −1·0 V(NHE)/Hg	40%	10%

Matschiner and Rudorf[115] have investigated the mechanism of electrochemical reduction of oxoketene dithioacetals and reported preparative scale electrochemical carboxylation of these intermediates to give 2-alkylthio-3-acyl-acrylic acids **121** as useful building blocks in organic synthesis (Scheme 20). Recently Steckhan and co-workers[114] have also reported the electroreduction of cyclic dithioacetals **115**, in the presence of carbon dioxide to afford the corresponding carboxylate anions,

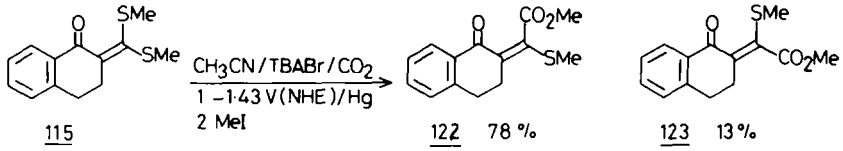


117 118 119 120 121

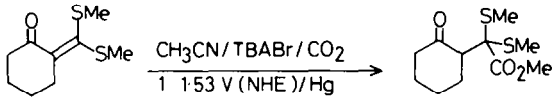
R	R	% yield
Me	H	50
C_6H_5	H	60
4-$MeOC_6H_4$	H	66
4-ClC_6H_4	H	70
2-Furyl	H	50
C_6H_5	Me	50
		40

Scheme 20.

which are trapped as methyl esters after treatment with methyl iodide (eq. 27). The corresponding 2-bis(methylthio) methylene cyclohexanone undergoes cathodic reduction in the presence of CO_2 to give the addition product **124** (eq. 28).[114]



115 122 78 % 123 13 % (27)

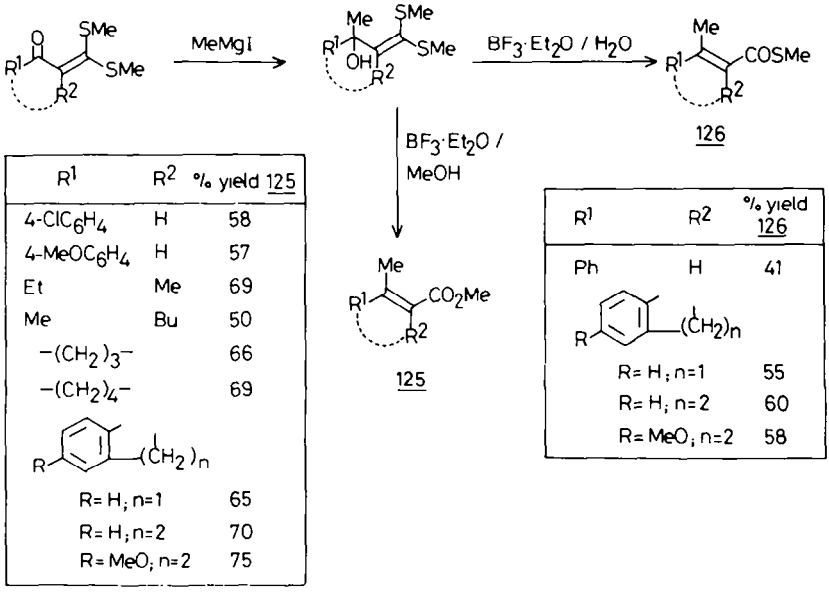


113 124 40 % (28)

5. C–C BOND FORMATION REACTIONS

5.1. *C–C Bond formation reactions and alkylative 1,3-carbonyl transpositions*

Extensive studies made on 1,3-alkylative carbonyl transpositions involving 1,2-addition of organometallic reagents either on vinylogous thiol esters or on α-oxoketene dithioacetals to afford intermediate carbinolacetals in high yields and their subsequent acid induced transformations to α,β-unsaturated thiolesters have been reviewed by Dieter.[116] Subsequently Junjappa[117] and Ila have investigated the reaction of methylmagnesium iodide on α-oxoketene dithioacetals to afford the expected carbinolacetals by 1,2-addition in good yields. The BF_3-etherate assisted methanolysis of these carbinolacetals afforded the corresponding β-methyl-α,β-unsaturated esters **125** as exclusive *E*-stereoisomers (Scheme 21). The corresponding α,β-unsaturated thiolesters **126** could also be

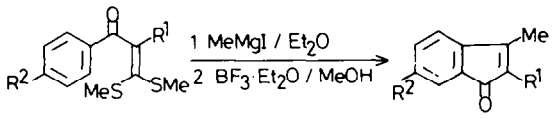


R^1	R^2	% yield 125
4-ClC_6H_4	H	58
4-$MeOC_6H_4$	H	57
Et	Me	69
Me	Bu	50
$-(CH_2)_3-$		66
$-(CH_2)_4-$		69
R= H; n=1		65
R= H; n=2		70
R= MeO; n=2		75

R^1	R^2	% yield 126
Ph	H	41
R= H; n=1		55
R= H; n=2		60
R= MeO; n=2		58

Scheme 21.

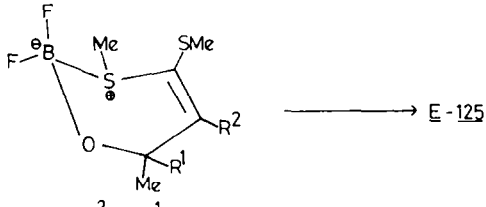
obtained under hydrolytic conditions in moderate to good yields. The carbinolacetals derived from α-alkyloxoketene dithioacetals of higher homologues of acetophenone, on the other hand, yielded the corresponding 2-alkyl-3-methylindenones **127** (eq. 29) under identical solvolytic conditions.



127 (29)

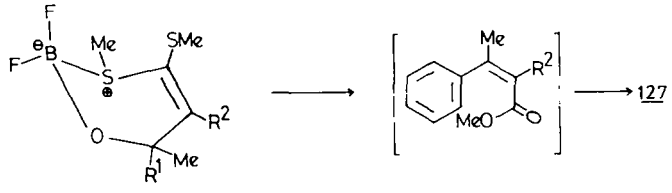
R^1	R^2	% yield 127
Me	H	55
Me	Me	60
Et	H	50
Et	MeO	57
n-Pr	H	62
n-Pr	MeO	56

The mechanism proposed by Junjappa and Ila[117] involves boat-like transition states **128** and **129** corresponding to *E* and *Z* cinnamates respectively (eq. 30 and 31). When R^2 = H as in **128**, the bulkier phenyl group (R^1) occupies the quasiequatorial position leading to *E*-cinnamates, while when R^2 is the bulkier group, the methyl group occupies the quasiequatorial position as in **129**, which ensures a minimum 1,2-repulsive interaction, leading to *Z*-cinnamates **125** which are the actual precursors for indenones **127** (eq. 31).



E-125 (30)

128, R^2 = H ; R^1 = aryl

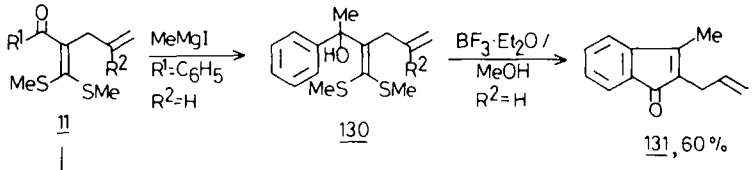


127 (31)

129, R^2 = alkyl ; R^1 = aryl

The alkylative 1,3-carbonyl transposition methodology was also further extended to α-alkenyl-α-oxoketene dithioacetals (eq. 32 and 33).[111] The carbinolacetal **130** obtained by addition of methylmagnesium iodide to α-aroyl-α-allylketene dithioacetal **11** ($R^1 = C_6H_5$: R^2 = H) underwent BF_3-etherate assisted methanolysis to afford 2-allylindenone **131** presumably through the intermediate transition state **129** (R^2 = allyl; $R^1 = C_6H_5$) described in eq. 31. However, the carbinolacetals

derived from α-acylalkenyl ketene dithioacetals **11** (R^1 = Me; R^2 = H, Me), where the aromatic participation is absent, yielded under identical conditions, the corresponding γ,δ-unsaturated ene-esters **132** and **133**. These esters on treatment with the phosphoric acid/formic acid mixture afforded the corresponding α-isopropylidene-γ-butyrolactones **134** and **135** respectively, in good yields (eq. 32, 33).



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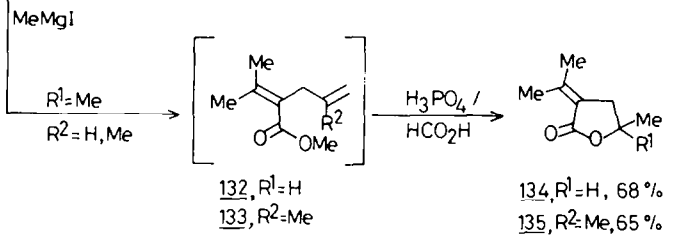
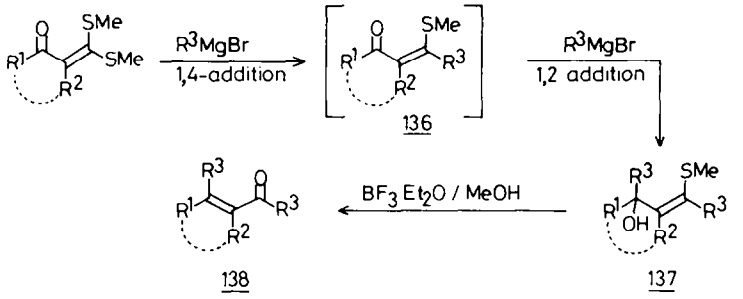
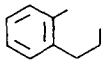
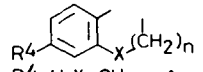


(33)

The course of addition of higher alkyl Grignard reagents (R^3 = Et, n-Pr, n-Bu) to oxoketene dithioacetals followed a sequential 1,4- and 1,2-addition pattern to afford carbinolacetals **137** and α,β-unsaturated ketones **138** after subsequent methanolysis under the conditions described[117] (Scheme 22). Similarly, phenylmagnesium bromide followed the identical course as above to yield the corresponding α,β-unsaturated ketones[117] (Scheme 22).



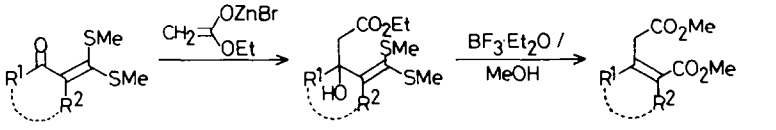
R^1	R^2	R^3	% yield 138
$-(CH_2)_4-$		Et	48
$-(CH_2)_4-$		n-Pr	50
$-(CH_2)_4-$		n-Bu	55
$-(CH_2)_3-$		n-Bu	53
		n-Pr	50
		n-Bu	55
C_6H_5	H	C_6H_5	71
4-MeC_6H_4	H	C_6H_5	64

R^1	R^2	R^3	% yield 138
4-MeOC_6H_4	H	C_6H_5	61
$-(CH_2)_4-$		C_6H_5	53
			
R^4=H, X=CH_2, n=1		C_6H_5	65
R^4=H, X=S, n=1		C_6H_5	62
R^4=Me, X=S, n=1		C_6H_5	67
R^4=Me, X=S, n=2		C_6H_5	62
R^4=H, X=O, n=2		C_6H_5	57

Scheme 22.

Although the high regioselectivity of C_6H_5MgBr can be attributed to its matching soft–soft nucleophile (C_6H_5MgBr)-electrophile (β-carbon) combination, the diminished regioselectivity of higher alkyl Grignard reagents was probably due to greater steric influence rather than electronic factors.

The 1,2-addition of an acetate unit to α-oxoketene dithioacetals has been reported to occur either by addition of ethyl bromozinc acetate[118] or lithioacetate[119] to afford intermediate carbinolacetals which are found to be useful intermediates for many interesting transformations. Thus BF_3-etherate assisted methanolysis of **138** obtained by addition of Reformatsky reagent[118a] derived from ethyl bromoacetate, yields propene dicarboxylates **140**, while iodine catalysed dehydration of **138** affords the corresponding polarised dienes **139** (Scheme 23). The overall transformation of oxoketene dithioacetal to **140** could be considered as a double 1,3-alkylative carbonyl transposition. The dienes **139** hold considerable promise as useful synthetic intermediates. They undergo ring closure to pyridones **141** (eq. 34) when heated with ammonium acetate.[118b] Interestingly, when oxoketene dithioacetals were reacted with bromozincacetate in the presence of cuprous (I) iodide the corresponding pyrones **142** were obtained in good yields (eq. 35). Dieter and co-workers have developed a general synthetic approach to substituted and annelated pyrones.[3,120] Their general scheme consists of 1,2-nucleophilic addition of ester, ketone and hydrazone enolate anions either to α-oxoketene dithioacetals or vinylogous thiolesters followed by acid promoted 1,3-carbonyl transposition and enollactonisation of the resulting δ-ketoacids or esters (eq. 36–38, Scheme 24, 25). These reactions allow introduction of alkyl substituents at all the four olefinic carbon atoms of the pyrone ring with



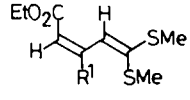
138 140

R^1	% yield 139
C_6H_5	70
4-MeC_6H_4	68
4-ClC_6H_4	55
4-BrC_6H_4	62
4-$MeOC_6H_4$	60
2-naphthyl	50
Me	45

I_2 / C_6H_6 / Δ

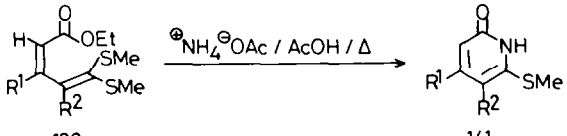
R^2 = H

R^1	R^2	% yield 140
C_6H_5	H	65
4-MeC_6H_4	H	70
4-$MeOC_6H_4$	H	63
4-ClC_6H_4	H	55
Me	H	50
	$-(CH_2)_4-$	60



139

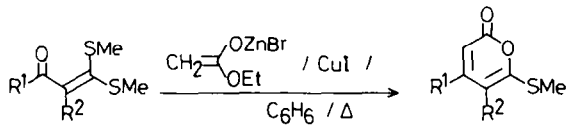
Scheme 23.



139 141 (34)

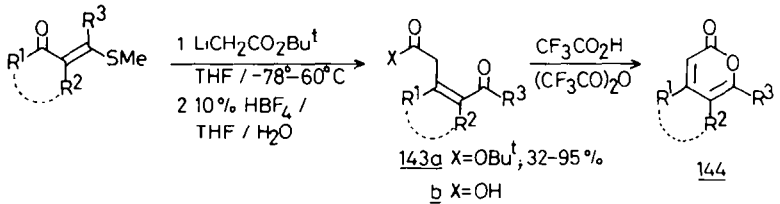
139, 141, R^1 = substituted aryl, Me; Ar–CH=CH–; R^2 = H

$R^1 = R^2$ = Me 60–70 %



142 (35)

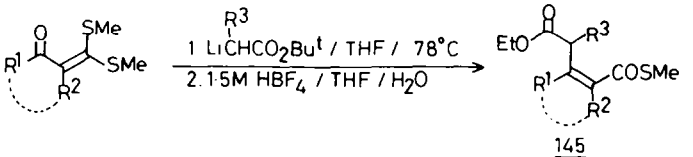
R^1	R^2	% yield 142	R^1	R^2	% yield 142
C_6H_5	H	63	Me	H	60
4-$MeOC_6H_4$	H	53	Me	Me	48
2-furyl	H	58			
2-thienyl	H	58			



143a X=OBu^t; 32–95 %
b X=OH

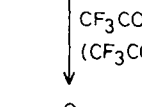
144 (36)

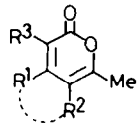
R^1	R^2	R^3	% yield 144	R^1	R^2	R^3	% yield 144
$-(CH_2)_3-$		H	80	Me	H	Me	72
$-(CH_2)_3-$		Me	93	Me	H	n-Bu	95
$-(CH_2)_3-$		s-Bu	70	Me	H	s-Bu	91
$-(CH_2)_4-$		Me	94	i-Pr	H	Me	92
		Me	99	Et	Me	H	49
				Et	Me	Me	91



145

R^1	R^2	R^3	% yield 146
$-(CH_2)_3-$		H	93
$-(CH_2)_4-$		H	85
$-(CH_2)_3-$		Me	87
Me	Et	Me	88

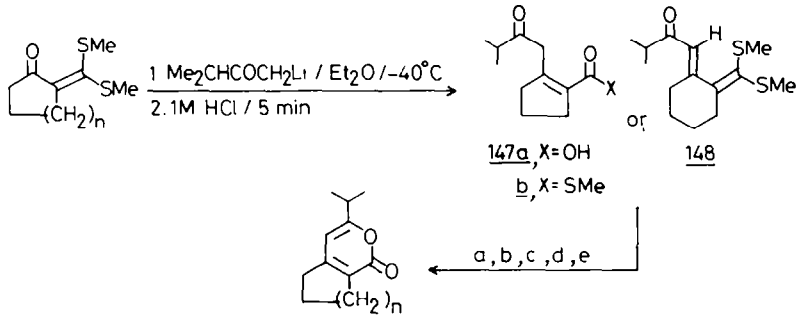




146 (37)

the limitation of 3-alkylpyrones, since it needs to utilise α-substituted acetate enolate anions. The required vinylogous thiolesters were prepared by chemoselective 1,4-addition of organocuprates to α-oxoketene dithioacetals and the details of these studies are discussed in the earlier review. An examination of the efficiency of *t*-butyl, methyl and trimethylsilyl acetate enolates show that the *t*-butyllithioacetate yields the best results with both cyclic and acyclic vinylogous thiolesters. In general, good yields of the corresponding δ-ketoesters **143a** and **145** were obtained by treatment of the resulting carbinols with 1.5 M HBF_4 (eqs 36 and 37). In some cases δ-ketoacids **143b** were obtained instead of the corresponding esters under these conditions.[3] The enol-lactonisation of these acids or esters were best achieved in the presence of a mixture of trifluoroacetic acid and its anhydride or at times with trifluoroacetic anhydride only to afford the corresponding α-pyrones **144** or **146** in excellent yields (eqs. 36 and 37). In some cases, the allyl alcohols obtained by the addition of lithioacetates underwent rearrangement, ester hydrolysis and enol-lactonisation directly to afford the corresponding α-pyrones in good yields.

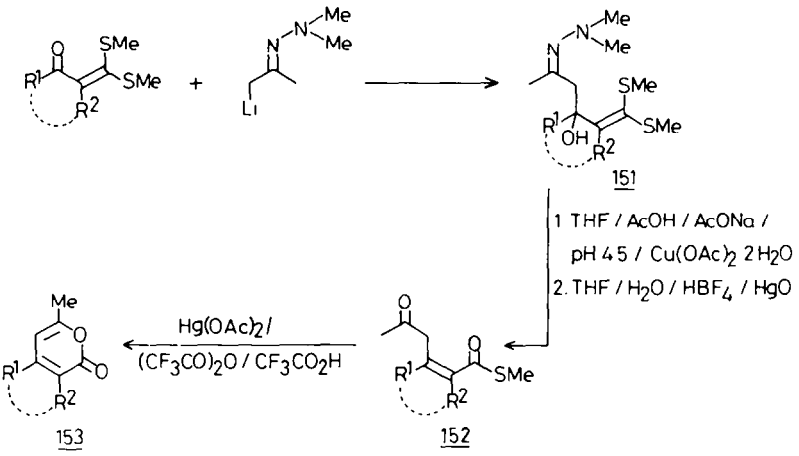
The extension of this method to ketone enolates suffered limitations by their reluctance to participate in aldol-type addition with other ketones. Thus the kinetic enolate of methylisopropyl



Scheme 24.

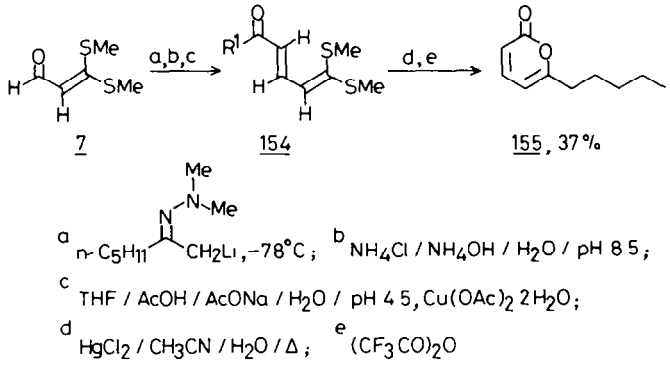
ketone underwent smooth 1,2-addition to dithioacetal derived from cyclopentanone, first to afford the carbinolacetal which on treatment with HCl and subsequent enol-lactonisation of δ-ketoester **147** gave the corresponding 6-isopropylpyrone **149** in good yields (Scheme 24).[3] The oxoketene dithioacetal from cyclohexanone, however, yielded the dienone **148** instead of carbinol on treatment with isopropylmethylketone enolate. The dienone **148** underwent cyclisation in the presence of HBF_4 to afford the cyclic pyrone **150** (Scheme 24) in moderate yields.[3]

The acyclic ketene dithioacetals, on the other hand, gave poor yields of addition products when treated with enolate anions of methylisopropyl ketones, 3-pentanone or cyclohexanone. This problem was circumvented by the addition of the corresponding hydrazone enolate anion to give the adducts **151** which could be hydrolyzed and rearranged in a one-pot reaction either by sequential addition of $Cu(OAc)_2$ and HBF_4/HgO (**151a** and **151b**) or by prolonged stirring with trifluoroacetic acid (**151c**).[3] The resulting esters **152** underwent smooth cyclisation to pyrones **153** in excellent yields under typical conditions (Scheme 25). Similarly, 6-pentyl-2H-pyran-2-one **155**, a natural product found in peach, could be synthesised in 37% overall yield through dienone **154** by reacting dithioacetal **7**, derived from acetaldehyde, with the appropriate hydrazone enolate (eq. 38).[3]



151-153	R^1	R^2	% yield 153
a	$-(CH_2)_3-$		75–78
b	$-(CH_2)_4-$		73
c	Et	Me	80

Scheme 25.

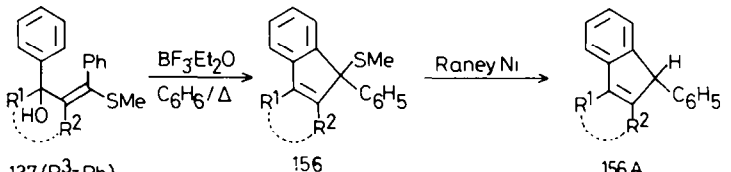


(38)

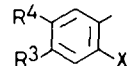
5.2. 1,2 *C-C Bond formation reactions and cyclisation reactions*

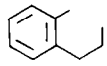
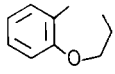
Singh, Ila and Junjappa[121] observed that the carbinol-acetals **137** (R^3 = Ph), obtained by sequential 1,4- and 1,2-addition of phenylmagnesium bromide to oxoketene dithioacetals, underwent BF_3-etherate assisted cyclisation to afford the corresponding 1-methylthio-1-phenylindenes **156** in moderate to good yields (Scheme 26). Some of the indenes were desulphurised in the presence of Raney nickel to give 1-phenylindenes (Scheme 26).

In continuation of these studies on new C–C bond forming reactions by addition of carbon nucleophiles to α-oxoketene dithioacetals, Junjappa and Ila[122] first reported the reaction of allylmagnesium bromide on **1** to afford carbinolacetals **157** exclusively in nearly quantitative yields (eq. 39). The carbinols **157** thus obtained underwent facile cycloaromatisation in the presence of BF_3-



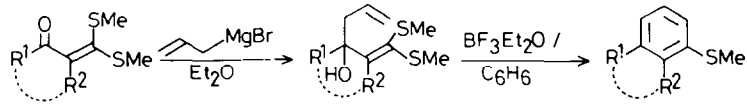
137 (R^3=Ph) 156 156A

R^1	R^2	% yield 156
C_6H_5	H	67
C_6H_5	CH_3	71
		
X=CH_2; n=1; R^3=R^4=H		54
X=S; n=1; R^3=R^4=H		72
X=S; n=2; R^3=Me, R^4=H		76
X=S; n=2, R^3=H, R^4=Me		71
X=O; n=2; R^3=R^4=H		68

R^1=Ph R^2=H 48%
R^1=Ph R^2=Me 56%
R^1=R^2=  29%
R^1=R^2=  51%

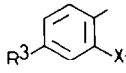
Scheme 26.

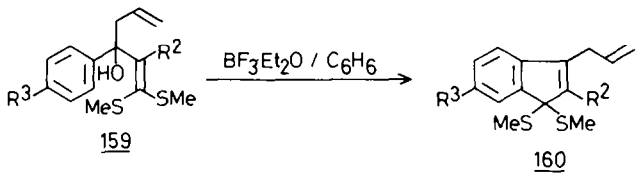
etherate in refluxing benzene to afford arylthiomethylethers **158** in good yields (eq. 39). The reaction is a direct entry from highly functionalised open-chain precursors to appropriately substituted aromatics in a simple two-step reaction sequence. The reaction was found to be general with oxoketene dithioacetals derived from both cyclic and acyclic ketones (eq. 39), though yields in the latter cases were moderate. Soon after this publication, Dieter and co-workers[123] also published



(39)

157 158

R^1	R^2	% yield 158
$-(CH_2)_4-$		74
$-(CH_2)_3-$		64
		
R^3=H, X=CH_2, n=0		54
R^3=H, X=CH_2, n=1		68
R^3=MeO, X=CH_2, n=1		67
R^3=H; X=S, n=1		59
R^3=H; X=S, n=2		67
R^3=H; X=O; n=2		64
C_6H_5	H	45
4-$MeOC_6H_4$	H	39
4-ClC_6H_4	H	40
Et	Me	40

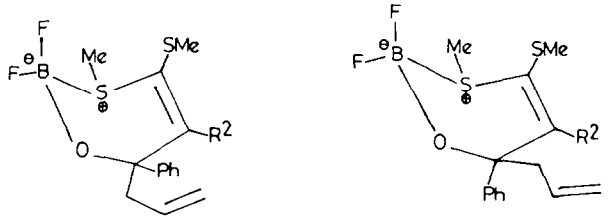


159 160 (40)

R^2	R^3	% yield 160
Me	H	80
Et	H	71
n-Pr	H	76
n-Pr	MeO	79

identical results by reacting methylallylmagnesium bromide with oxoketene dithioacetals to afford methylsubstituted phenylthioethers.

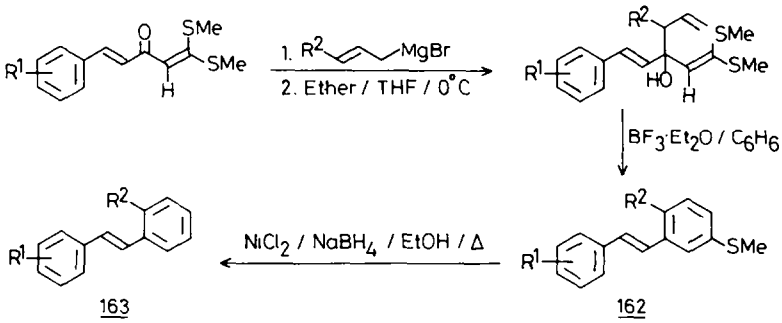
The α-alkyl-α-oxoketene dithioacetals, on addition of allylmagnesium bromide, yielded the expected carbinol-acetals **159** in high yields. However, when these eneacetals were treated with BF_3-etherate in benzene, the corresponding 3-allyl-1,1-bis(methylthio)-2-alkylindenes **160** were formed (eq. 40) instead of the corresponding cycloaromatised products.[124] The formation of either aromatic product or indenes **160** can be explained through the cyclic transition states **161A** and **161B** respectively (Fig. 1). When R^2 = H or $R^1 = R^2 = -(CH_2)_n-$, the allyl group occupies the quasi-axial position and could interact with the bis(methylthio) methylene double bond to afford cyclo-aromatized products. However, when R^2 = alkyl, $R^1 = C_6H_5$, the phenyl group occupies the quasi-axial position (**161B**) in order to minimise steric interaction between 1,2-substituents, so that the aromatic π-cloud can attack the developing cation stabilised by the bis(methylthio) functionality to afford 3-allylindenes **160**.[124]



161A, R^1=H 161B, R^1=alkyl

Fig. 1.

Asokan, Ila and Junjappa[125] reacted allylmagnesium bromide with α-cinnamoylketene dithio-acetals and treated the intermediate carbinolacetals with BF_3-etherate, when the 3-methylthio-stilbenes **162** (Scheme 27) were formed through cycloaromatisation. The reaction constitutes a novel entry to substituted stilbenes through construction of one of the aromatic rings from acyclic precursors. However, the method failed when extended to homologous 5-aryl-2,4-pentadienoyl-ketene dithioacetals to afford 1,4-diarylbutadienes.



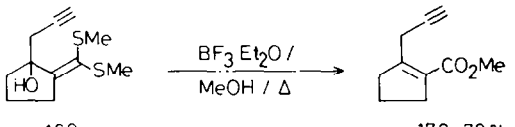
R^1	R^2	% yield 163
H	H	59
4-Me	H	61
4-Cl	H	62
H	Me	60

R^1	R^2	% yield 162	R^1	R^2	% yield 162
H	H	68	2,6-Cl_2	H	52
4-Me	H	62	3,4-Cl_2	H	53
4-Cl	H	68	H	Me	52
3-MeO	H	57	4-Me	Me	51
2-Cl	H	61	4-Cl	Me	51

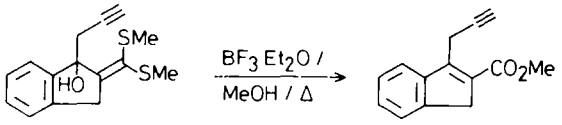
Scheme 27.

Subsequently, this method of aromatic annelation was extended to naphthoannelation, by Junjappa, Ila and co-workers.[126] The strategy to achieve this transformation was conceived by reacting benzylmagnesium chloride with α-oxoketene dithioacetals to afford the intermediate carbinolacetals, which on treatment with BF_3-etherate should yield the corresponding naphthalene derivatives through benzene ring participation. However, when the cyclic oxoketene dithioacetal derived from cyclohexanone [$R^1 = R^2 = —(CH_2)_4—$] was reacted with benzylmagnesium chloride (1.2 equiv.), the product isolated (31%) after treatment with BF_3-etherate was characterised as 9-benzyl-1,2,3,4-tetrahydroanthracene (**164**), while 35% of the starting material was recovered. Apparently, two equivalents of benzylmagnesium chloride were added sequentially in 1,4- and 1,2-manner resulting in low (31%) yield of tetrahydroanthracene which was raised to 81% when 3 equiv. of $C_6H_5CH_2MgCl$ was used and no starting material was recovered. Many substituted naphthalenes and other fused aromatics were thus prepared in good yields following this route (Scheme 28).

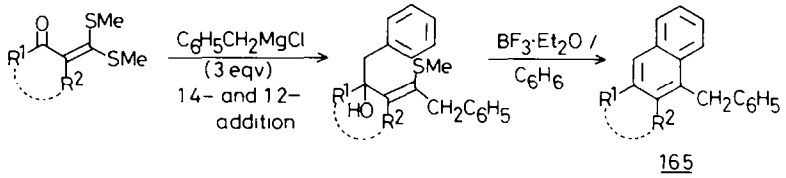
The propargylmagnesium bromide also underwent exclusive 1,2-addition to α-oxoketene dithioacetals yielding carbinolacetals **166** in high yields. Here again, the carbinols **166** were conceived to undergo cationic ring closure to afford methoxysubstituted benzoannelated products **168** (Scheme 29).[127] The reaction was proved to be of general synthetic application when applied to many structural variants of cyclic α-oxoketene dithiacetals to yield fused methoxy substituted aromatics (Scheme 29). The thiomethyl group can be removed by Raney nickel desulphurisation at the end of the reaction. However, the carbinolacetals derived from cyclopentanone dithioacetal failed to undergo benzoannelation and the product was identified as β-propargyl-α,β-unsaturated ester **170** (eq. 41). Similarly the carbinolacetal **171** yielded, under the described reaction conditions, the corresponding 2-methoxycarbonyl-3-propargyl indene **172** (eq. 42).



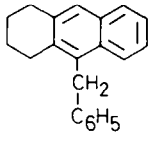
169 170, 78% (41)



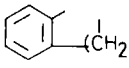
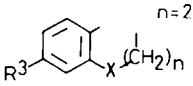
171 172, 82 % (42)



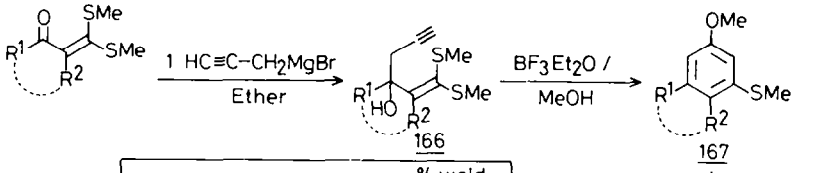
165



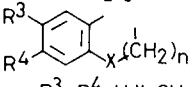
164

R^1	R^2	% yield 165
	n=1	62
	n=2	71
		
R^3 = H, X=S, n=1		58
R^3 = Me, X=S, n=2		68
R^3 = H, X=O, n=2		67
C_6H_5	H	59
4-$MeOC_6H_4$	H	61
4-MeC_6H_4	H	65
2-naphthyl	H	58

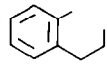
Scheme 28.



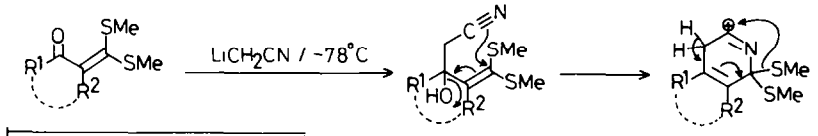
166 167

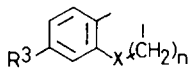
R^1 R^2	% yield 167
$-(CH_2)_4-$	76
$-(CH_2)_5-$	71
	
R^3=R^4=H, X=CH_2, n=1	78
R^3=H, R^4=MeO, X=CH_2, n=1	66
R^3=H, R^4=Me, X=CH_2, n=1	77
R^3=R^4=H, X=S, n=1	72
R^3=Me, R^4=H, X=S, n=1	68
R^3=R^4=H, X=S, n=2	69
R^3=Me, R^4=H, X=S, n=2	81
R^3=R^4=H, X=O, n=2	75

168 a R^1=R^2=$-(CH_2)_4-$

b R^1=R^2= 

Scheme 29.

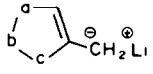


R^1	R^2	% yield 174
C_6H_5	H	82
2-naphthyl	H	79
2-thienyl	H	75
2-furyl	H	71
3-pyridyl	H	77
Me	H	78
Me	Me	68
$-(CH_2)_4-$		76
		
X=CH_2; R^3= H; n=1		83
X=S; R^3= Me; n=2		79

Scheme 30.

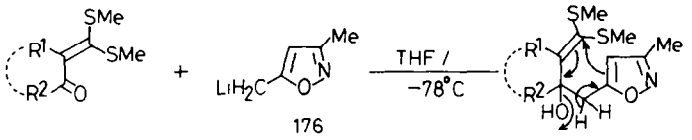
The strategy of external nucleophile participation was considered of interest in the addition of lithioacetonitrile to α-oxoketene dithioacetals to give carbinolacetals **173** in which the nitrogen atom is so positioned that it can participate in the new C–N bond formation so that the ring closure should yield the corresponding pyridine derivative instead of aromatic systems under analogous conditions. Thus the carbinols **173** obtained in high yields smoothly underwent ring closure in the presence of phosphoric acid (88%) to afford 2,6-bis(methylthio)-3,4-substituted and fused pyridine derivatives **174** in good yields[128] (Scheme 30). However, in the presence of BF_3-etherate, the oxoketene dithioacetal derived from acetophenone ($R^1 = C_6H_5$; $R^2 = H$) afforded only the diene **175** (Scheme 30) instead of pyridine. The mechanism is proposed to involve either intermolecular or intramolecular migration of methylthio group and ring closure through intramolecular Ritter-type reaction (Scheme 30).[128] The flexibility of structural variation in α-oxoketene dithioacetals is demonstrated by selection of both acyclic and cyclic derivatives to afford substituted and annelated pyridines in 68–83% overall yields (Scheme 30).

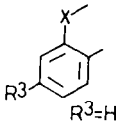
Junjappa and co-workers extended their aromatic annelation methodology to yet another interesting heteroaromatic system, where the aromatic ring can be constructed over preconstructed five-membered heterocycles by reacting the α-oxoketene dithioacetals with lithioalkyl systems of the general formula **176**. Thus the reaction of 3-methyl-5-lithiomethylisoxazole with α-oxoketene dithio-

 **176**

acetals afforded exclusive 1,2-carbinol-acetals **177** which on treatment with BF_3-etherate gave the corresponding benzisoxazoles **178** in 54–81% overall yields **1** (Scheme 31). In principle, the construction of aromatic ring over many other heterocycles should be possible and the success of this strategy depends upon the ease with which one can develop lithiomethylheterocycles which are often not generated by direct deprotonation of the corresponding methyl substituted heterocycles.

Balu, Ila and Junjappa[130] have also investigated the reaction of heteroallyl systems with α-oxoketene dithioacetals with a view to enhancing the scope of their aromatic annelation methodology for the synthesis of heteroaromatic systems. As a part of this general synthetic strategy the 2-

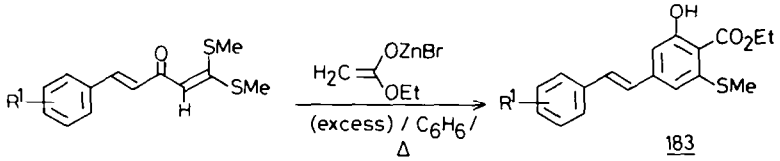


R^1	R^2	% yield 178
C_6H_5	H	73
4-ClC_6H_4	H	66
4-$MeOC_6H_4$	H	68
β-naphthyl	H	64
Me	H	54
2-furyl	H	59
2-thienyl	H	61
$-(CH_2)_4-$	H	65
$-(CH_2)_5-$	H	67
		
R^3=H X=CH_2		57
R^3=H X=$-(CH_2)_2-$		76
R^3=Me X=$-S(CH_2)_2-$		81

Scheme 31.

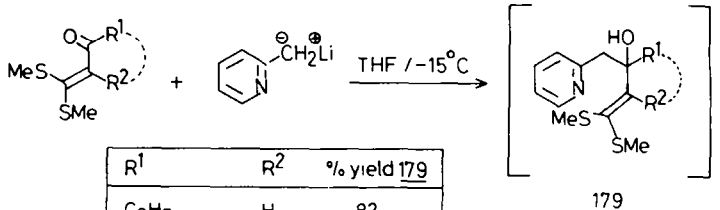
picolyllithium was reacted with α-oxoketene dithioacetals to afford 1,2-carbinol adducts **179** in high yields, which on treatment with BF_3-etherate afforded the corresponding substituted and fused quinolizinium fluoborates **180** in high yields[130] (Scheme 32). The method can open useful new avenues for the synthesis of many important alkaloids belonging to the isoquinoline, indole and protoberberine groups.

As a further development in this important aromatic annelation investigations, Datta, Ila and Junjappa[131] studied the reaction of ethyl zincbromoacetate on the diene **139** (Scheme 33) to afford the corresponding trienezincenolate which underwent facile electrocyclic ring closure followed by elimination of methylmercaptan to give the regiospecifically substituted and annelated 2-hydroxy-6-methylthiobenzoates **181** (Scheme 33) or the corresponding salicylates **182** after desulphurisation. The entire reaction sequence can also be accomplished in a one-pot reaction by directly reacting an excess of zincbromoacetate with oxoketene dithioacetals to afford **181** in identical yields.[131] The corresponding 3-hydroxy-5-methylthiostilbene-4-carboxylates (**183**) were similarly obtained in high yields by reaction of cinnamoylketene dithioacetals[131b] with excess ethyl zinc bromoacetate under identical conditions (eq. 43).



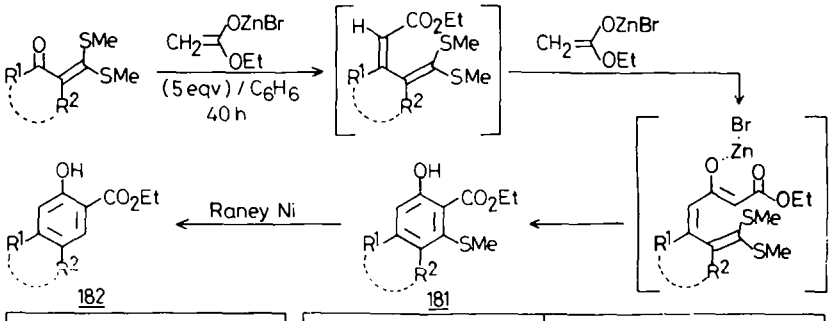
(43)

183, R^1 = H; 4-Me; 4-MeO; 4-Cl; 2,6-Cl_2; 3,4-$(MeO)_2$ 3,4,5-$(MeO)_3$; 4-NO_2; 60-74 %



R^1	R^2	% yield 179
C_6H_5	H	82
4-MeC_6H_4	H	84
4-$MeOC_6H_4$	H	84
β-naphthyl	H	73
2-furyl	H	76
2-thienyl	H	78
$-(CH_2)_4$	H	82
$-(CH_2)_5$	H	79
R^3= H; X= CH_2; n=1		85
R^3= MeO; X= CH_2; n=1		83
R^3= Me; X= CH_2; n=1		78
R^3= Me; X= S; n=2		80
R^3= H; X= O; n=2		81

Scheme 32.



R^1	R^2	% yield 182
Me	H	84
4-ClC_6H_4	H	88
	$-(CH_2)_4-$	76
	$-(CH_2)_5-$	79
R= H; n=1		63
R= OMe; n=2		81

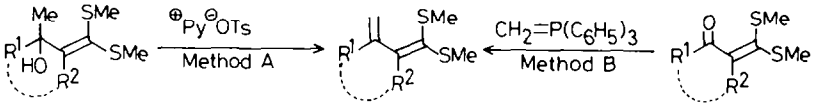
R^1	R^2	% yield 181
Me	H	60
4-ClC_6H_4	H	63
C_6H_5	H	60
2-Thienyl	H	63
2-Furyl	H	58
Me	Me	32
$-(CH_2)_3-$		52

R^1	R^2	% yield 181
	$-(CH_2)_4-$	57
	$-(CH_2)_5-$	60
R^3= H; n=1		55
R^3= MeO; n=2		58

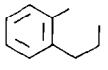
Scheme 33.

5.3. 1,2 *C C Bond formation: miscellaneous*

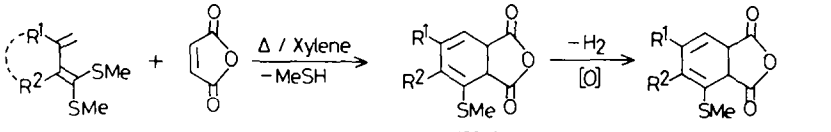
The 1,2-addition of dimethylsulphonium methylide to vinylogous thiolesters and α-oxoketene dithioacetals leading to the synthesis of butenolides and furans via intermediate epoxides[88,132] has been discussed in the earlier review. The α-oxoketene dithioacetals have been reacted with Wittig reagents to afford 1,1-bis(alkylthio)-1,3-dienes.[133] Similarly Junjappa and Ila[134] have prepared the acyclic and cyclic vinylketene dithioacetals **184** by reacting the respective oxoketene dithioacetals either by a 1,2-addition elimination sequence of methylmagnesium iodide (Method A) or by Wittig reagent, in good yields (Scheme 34). The potential of these vinylketene dithioacetals as 1,3-dienes in Diels–Alder reaction has been examined by reacting them with maleic anhydride and acetylene dicarboxylate (Scheme 35). Thus with maleic anhydride, the corresponding substituted and



184

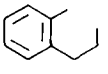
R^1	R^2	Method	% yield 184
Me	H	A	88
C_6H_5	H	A	86
4-MeC_6H_4	H	A	92
4-ClC_6H_4	H	A	90
4-$MeOC_6H_4$	H	A	92
Me	Me	A	89
		A	90
Et	Me	B	86
	$-(CH_2)_4-$	B	90

Scheme 34.

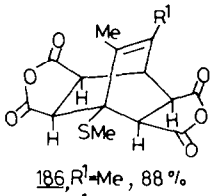


185 A

185

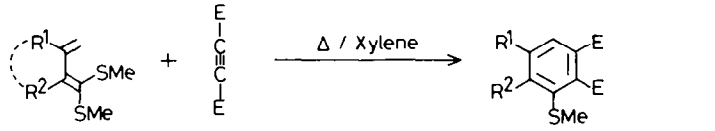
R^1	R^2	% yield
Me	H	68
C_6H_5	H	72
4-MeC_6H_4	H	66
4-ClC_6H_4	H	69
4-$MeOC_6H_4$	H	62
		71
	$-(CH_2)_4-$	76

R^1=Me, Et
R^2=Me



186, R^1=Me, 88 %
187, R^1=Et, 86 %

Scheme 35.



(44)

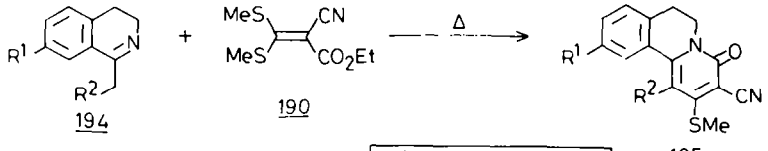
188, R^1=Me; R^2=H, 74%
189, R^1=R^2=Me, 67 %

fused phthalic anhydrides **185** were obtained through elimination of MeSH and subsequent dehydrogenation of [4+2] cycloadducts. With some 2,3-dialkyldienes the initial dihydrophthalic anhydrides **185A** underwent further [4+2] cycloaddition with a second mole of maleic anhydride to afford bicyclic adducts **186** and **187** instead of aromatised products (Scheme 35). Similarly, with dimethylacetylene dicarboxylate, the alkylphthalates **188** and **189** were formed (eq. 44). However, these dienes were found to be unreactive towards weaker dienophiles like acrylonitrile, ethyl acrylate and methylvinyl ketones.

5.4. 1,4-*Conjugate addition of carbon nucleophiles and cyclisation reactions*

Like α,β-unsaturated ketones, the β-alkylthio and β,β-bis(alkylthio)enones and enoates exhibit differential electrophilicity between β-carbon and carbonyl carbon atoms. In general, under normal reaction conditions the carbonyl carbon can be viewed as a hard electrophile and the β-carbon as a soft electrophile. The attacking carbon nucleophiles have accordingly displayed regioselectivity which can be broadly classified into hard and soft nucleophiles. Thus organolithium[135,106] methyl Grignard[117] and Reformatsky reagents[118] have shown high 1,2-regioselectivity as hard nucleophiles. However, higher alkyl and polarised Grignard (C_6H_5MgBr and $C_6H_5CH_2MgBr$) reagents lack this regioselectivity, and attack in sequential 1,4 followed by 1,2 fashion resulting, after hydrolysis, in the corresponding α,β-unsaturated ketones. The typical carbon soft nucleophiles such as organocuprates have shown distinct 1,4-regioselectivity and have been extensively investigated by Dieter and co-workers[54,87,135a,136,138] and covered in detail in the earlier review. Many stabilised enolate anions have been similarly reacted with oxoketene dithioacetals which normally add in 1,4 fashion and these reactions were extensively investigated by Kobayashi and co-workers in the sixties and seventies.

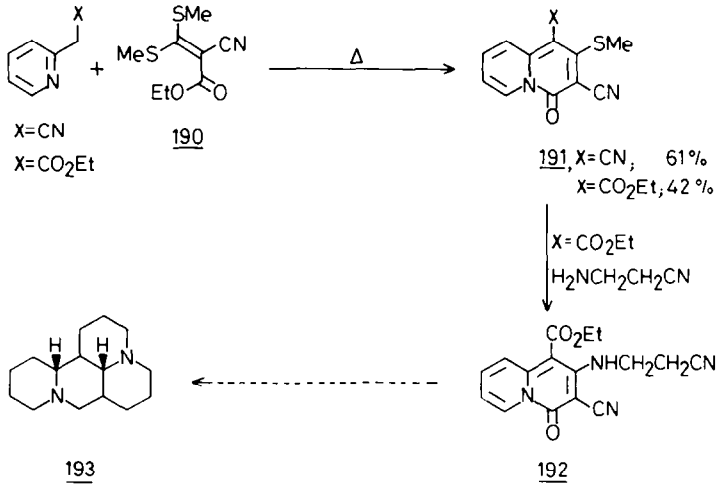
Depending on the functional group characteristics of the enolate anions and the structure of ketene dithioacetals, the 1,4-addition elimination combination may lead either to displacement of the methylthio group or to subsequent cyclisation to give a diverse product range. Thus α-pyridylacetonitrile/acetate,[139-141] on heating with dithioacetal **190** derived from ethyl cyanoacetate, yields quinolizones **191** in which the thiomethyl group is easily replaced by β-aminopropionitrile to give **192**, an intermediate in the synthesis of DL-allomedridine **193** (Scheme 36).[142] Condensation of dihydroisoquinolines **194** with cyanoacetate derived dithioacetal **190** similarly afforded the benzodihydroquinolizines **195** in good yields (eq. 45).[143] Similarly the nitroacrylates **197** or the



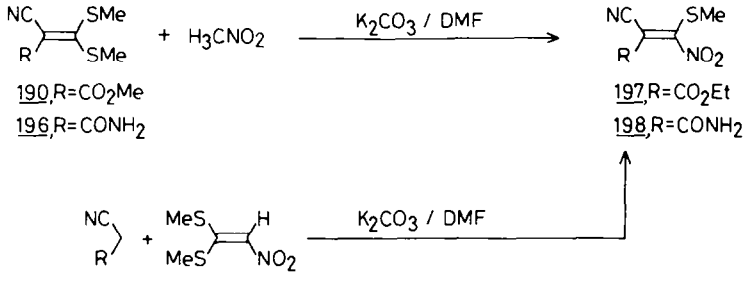
194 190 195

(45)

R^1	R^2	% yield 195
H	CN	80
H	CO_2Me	60
OMe	CN	80
OMe	CO_2Me	70



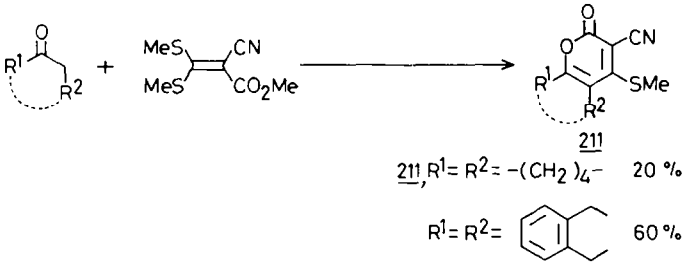
Scheme 36.



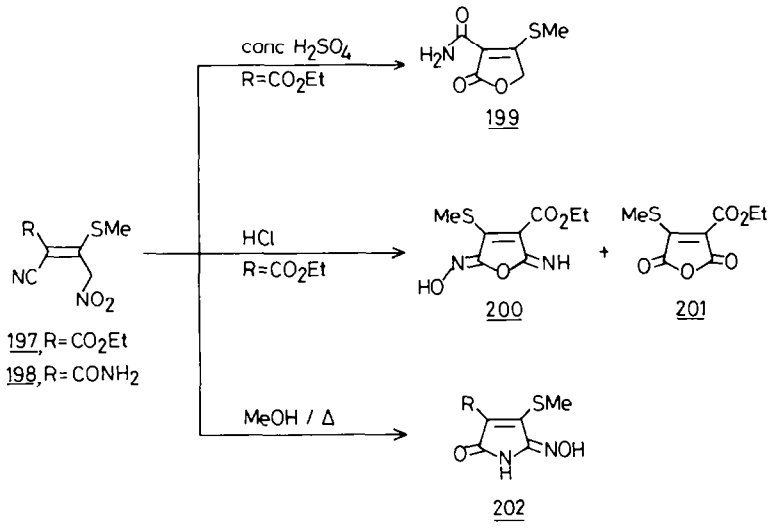
Scheme 37.

corresponding amides **198** could be obtained either by conjugate addition of enolates derived from cyanoacetate/amide to nitroketene S,S-acetal (Scheme 37)[144,145] or by conjugate addition of nitromethane enolate to ester **190** or **196**.

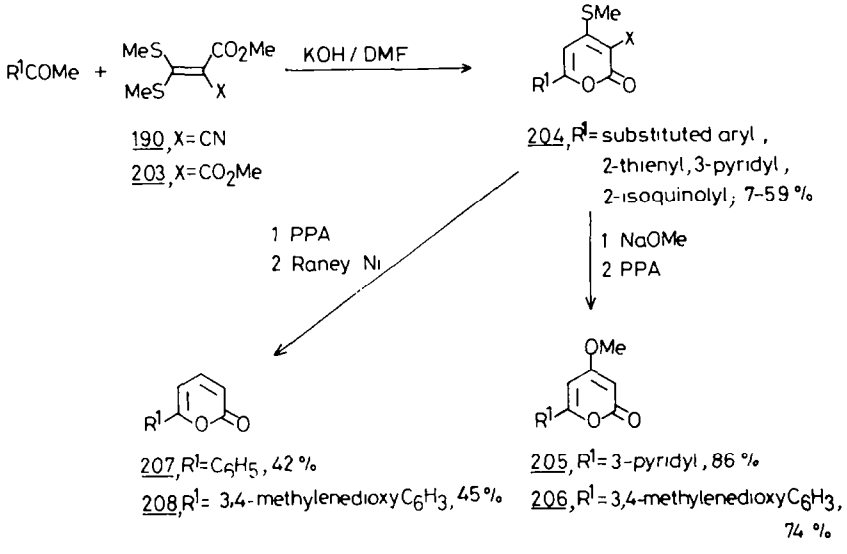
The addition products **197** and **198** were shown to undergo cyclisation to a number of five-membered heterocycles, under different reaction conditions, to afford butenolides (H_2SO_4) **199**,[146] furanone (HCl) **200**,[147] **201** and pyrrolinone **202**[146] in good yields (Scheme 38). Tominaga and other workers[148] have extensively investigated the addition of enolate anions derived from ketones to doubly activated ketene dithioacetals[148f] to afford 4-methylthio-2-pyrones **204** and **205** in low to moderate yields (Schemes 39, 40 and eq. 46). Some of these pyrones and styryl derivatives (Scheme



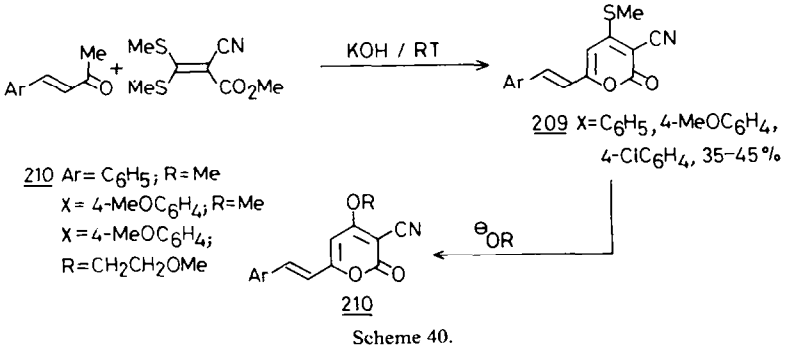
(46)



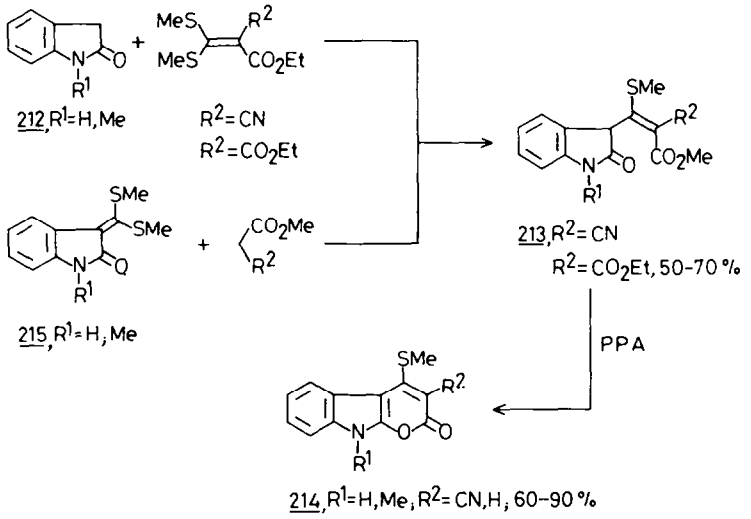
Scheme 38.



Scheme 39.



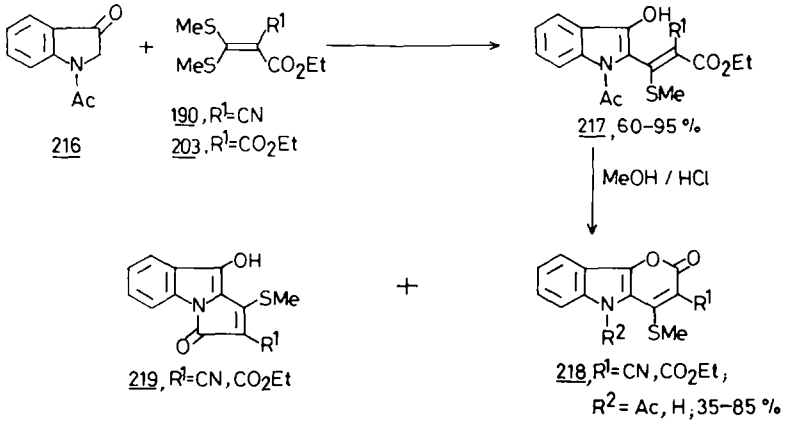
Scheme 40.



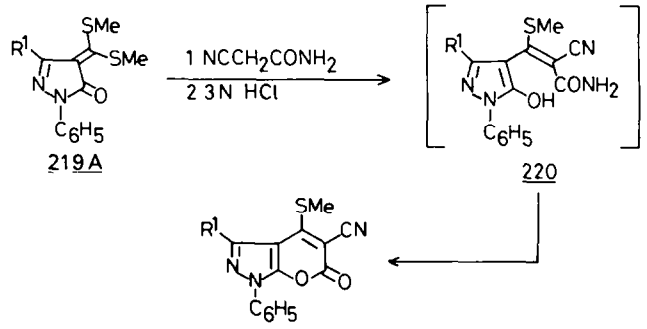
Scheme 41.

40) were found to be useful intermediates in the synthesis of naturally occurring pyrones like anibine **205**,[148c] phenylcoumalin **207**[148a] paracotoin (**208**),[148a] methoxyparacotoin **206**,[148a] 5,6-dihydrokowain[148d] and yangonin[148d] derivatives (Scheme 40). Conjugate addition of enolate anions derived from oxindoles (Scheme 41) to doubly activated ketene dithioacetals leads to adducts **213**, which undergo cyclisation in the presence of PPA to yield the condensed pyrones **214** (Scheme 41).[149-150]

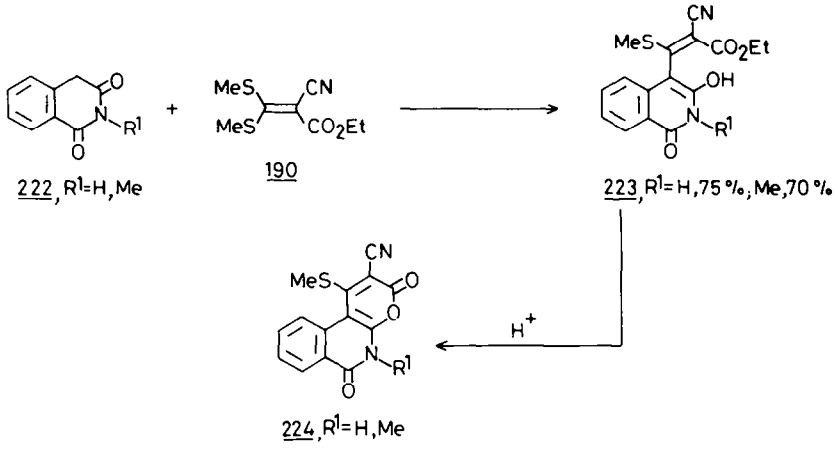
The alternative route for the synthesis of **213** is to add the enolate anion either from cyanoacetate or malonate to oxoketene dithioacetal **215** derived from oxindole.[151] Similarly the condensed isomeric pyrones **218** along with **219** could be obtained by cyclisation of **217** which in turn was prepared through addition of 3-indoxyl anion to dithioacetals **190** and **203** (Scheme 42).[152] Junjappa and Ila had similarly reported the synthesis of pyrano[2,3-*c*]pyrazoles **221** through conjugate addition of cyanoacetamide anion to ketene dithioacetals **219A** and subsequent acid catalysed cyclization of adducts **220** (Scheme 43).[61] Similarly the condensed pyrone **224** was obtained from 1,3-



Scheme 42.

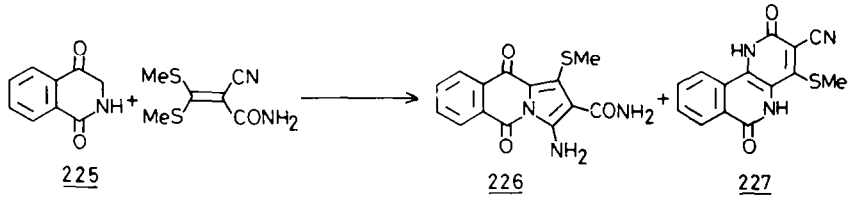


Scheme 43.



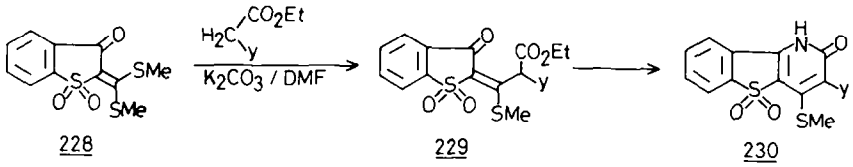
Scheme 44.

dioxotetrahydroisoquinoline **222** and **190** as depicted in Scheme 44.[150] The 1,4-conjugate addition of 1,4-dioxotetrahydroisoquinoline **225** with cyanoacetamide derived dithioacetal followed by cyclisation affords a mixture of pyrroloisoquinoline **226** and pyridoisoquinoline **227** (eq. 47).[153] Con-



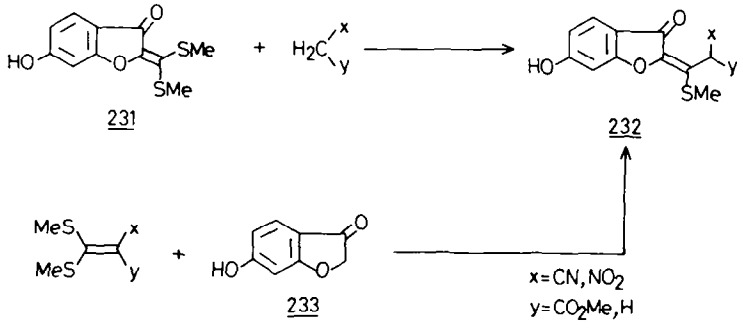
(47)

jugate additions of other heterocyclic ketones like coumaran-3-one and 3-ethylrhodamine to doubly activated ketene dithioacetals in the presence of various bases has also been reported. The same adducts have been obtained by an alternative route through 1,4-addition of the enolate anion of ethyl cyanoacetate to heterocyclic ketene dithioacetals (**228**, **231**, **234**) derived from coumaran-3-one, 3-ethylrhodamine and 3-oxobenzothiophene-1,1-dioxide[66,68,69] (eq. 48, 49, Scheme 45).



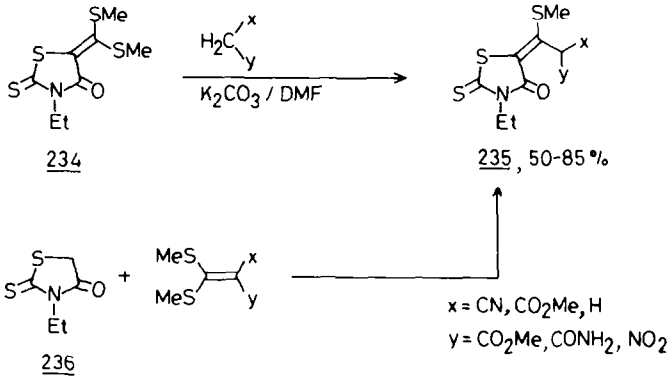
228 229 230 (48)

229, 230, y=CO_2Me, COMe



231 232 233

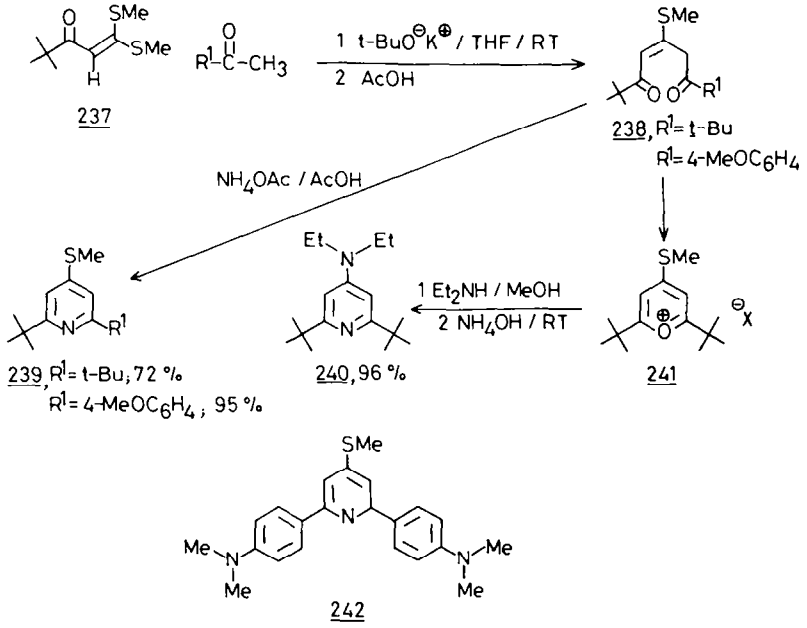
Scheme 45.



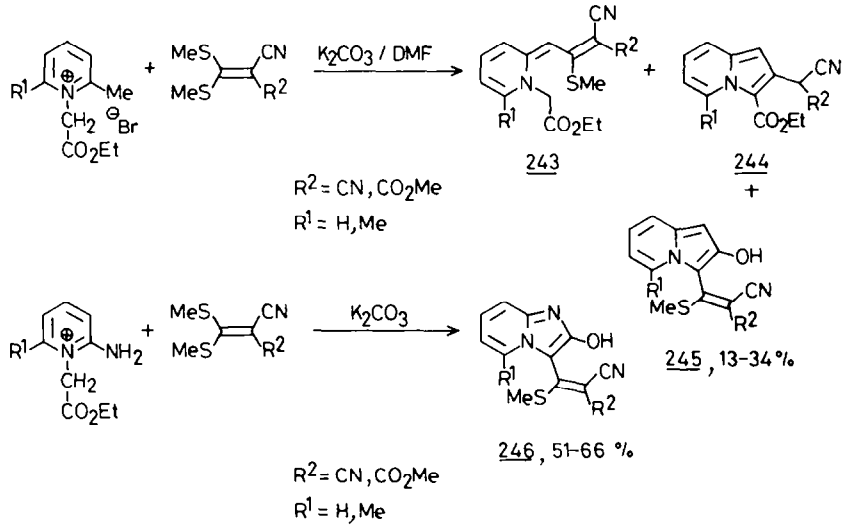
234 235, 50-85 % (49)

236

Potts and co-workers have extensively studied the conjugate addition of ketone enolates to α-oxoketene dithioacetals in the presence of potassium *t*-butoxide to afford 1,5-diones which were subsequently exploited for the synthesis of pyrilium salt and substituted pyridines. A number of simple, annulated pyridines, polypyridinyls and 2,6-furyl, thienyl substituted pyridines useful in the synthesis of macrocyclic polyether diesters containing these heterocyclic units have been synthesised using this strategy. These reactions have been discussed in detail in the earlier review.[13,14,154] Recently, Potts[155] extended this pyridine synthesis for the preparation of interesting bases such as 2,6-di-*t*-butyl-4-diethylaminopyridine (**240**) (Scheme 46) and other variants like **242** using oxoketene dithioacetal **237** derived from *t*-butylmethylketone (Scheme 46). Kobayashi and co-workers have investigated the addition of 2-methyl/2-amino pyridinium ylids to oxoketene dithioacetals as an efficient synthetic route to indolizine and imidazolopyridine derivatives (eq. 50, 51).[156]



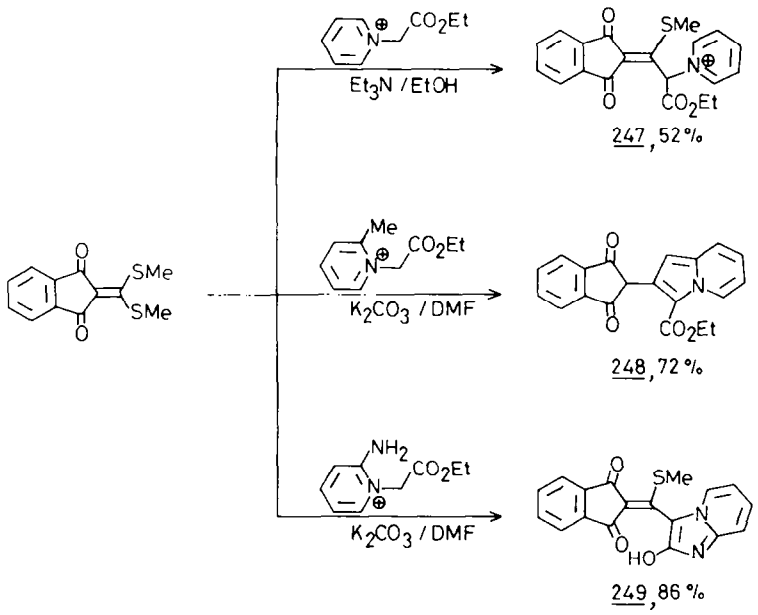
Scheme 46.



(50)

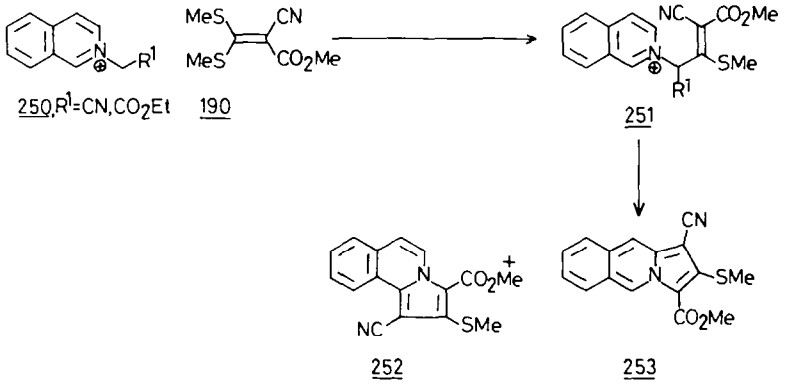
(51)

Tominaga and co-workers have further extended the conjugate addition of such pyridinium ylids to ketene dithioacetals derived from 1,3-indanediones (Scheme 47).[157] The reaction of isoquinolinium ylid **250** with doubly activated oxoketene dithioacetals affords pyrroloisoquinoline derivatives **252** and **253** apparently formed by 1,3-dipolar addition of **250** to the ketene dithioacetal double bond followed by elimination of methylmercaptan and carboxymethyl group (Scheme 48).[158] Interestingly, the sulphoxonium ylides undergo 1,4-addition followed by cyclocondensation at the carbonyl group of the oxoketene dithioacetals to afford substituted and annelated 1-methylthia-

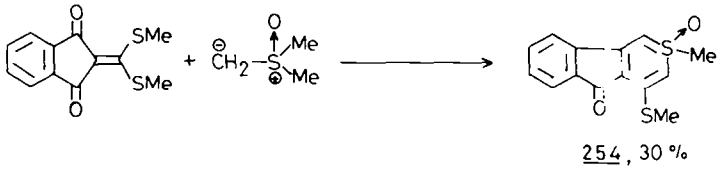


Scheme 47.

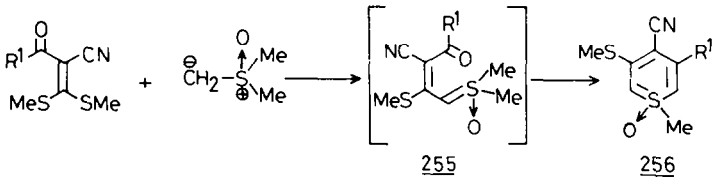
benzene-1-oxide derivatives (eq. 52 and 53).[157,159,160] Cyanide ion has also been used as a carbon nucleophile in the conjugate addition elimination sequence to α-oxoketene dithioacetals to afford β-cyano-α,β-unsaturated carbonyl compounds (eq. 54, 55). The synthetic potential of these reactions need further exploration.[161,69]



Scheme 48.



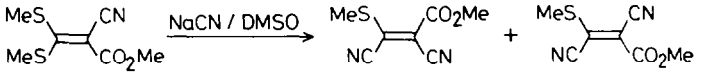
(52)



(53)

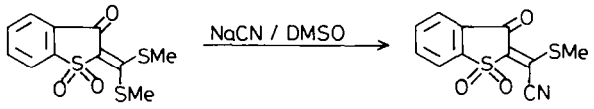
255 256

$R^1 = C_6H_5$; 4-BrC_6H_4; 4-ClC_6H_4, 3,4-$Cl_2C_6H_3$, 2-furyl
2-thienyl, cyclohexyl, styryl 43–73 %



(54)

257, 53 % (1:1)



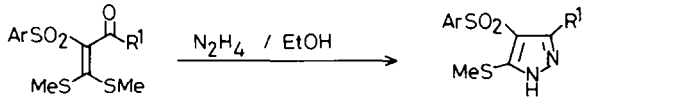
(55)

258

The conjugate addition of enolate anions to oxoketene dithioacetals may provide immense synthetic opportunities, provided the enolate anions are appropriately functionalised, so as to afford five- and six-membered carbo- and heterocycles.

6. REACTIONS WITH BIFUNCTIONAL HETERONUCLEOPHILES: SYNTHESIS OF HETEROCYCLES

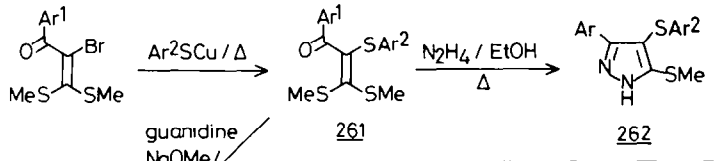
The α-oxoketene dithioacetals have been recognised as useful 3-carbon 1,3-electrophilic fragments which have been exploited extensively for the construction of five- and six-membered heterocycles. Some of their reactions with hydrazine,[162] hydroxylamine,[162a] guanidine, amidines,[8,162c,163] enamine, cyanoacetamide anions,[60,163,164] 1,2-diamine, 1,2-aminoalcohol and 1,2-aminothiols[58,165a] have been discussed in the earlier review. Subsequent developments involving their structural flexibility and reactivity with a variety of heteronucleophiles to afford a novel class of heterocycles have been covered in the present review. The new development in the pyrazole synthesis includes additional functionalisation and some interesting rearrangements. Thus 4-arylsulphonyl[166] and 4-arylthiopyrazoles[167] have been obtained by reacting hydrazine hydrate with the appropriate arylsulphonyl and arylthioketene dithioacetals (eq. 56 and Scheme 49). Junjappa and Ila have



(56)

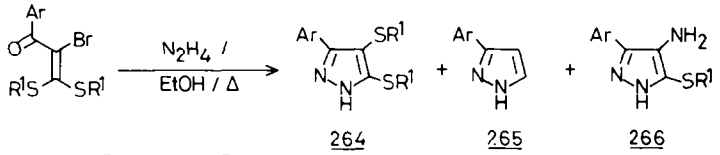
259 260, R^1=Me, 85 %
R^1=Ph, 88 %

observed an interesting 1,2-alkylthio shift during the reaction of α-bromo-α-oxoketene dithioacetals[168] with hydrazine hydrate to afford a mixture of pyrazoles **264**–**266** in varying yields (eq. 57).[169] The formation of these pyrazoles has been rationalised through episulphonium ion intermediate **270** via sulphur assisted elimination of bromine in the initially formed Michael adduct **269** (Scheme 50). Thus the intramolecular ring opening of **270** accompanied by a 1,2-alkylthio shift and



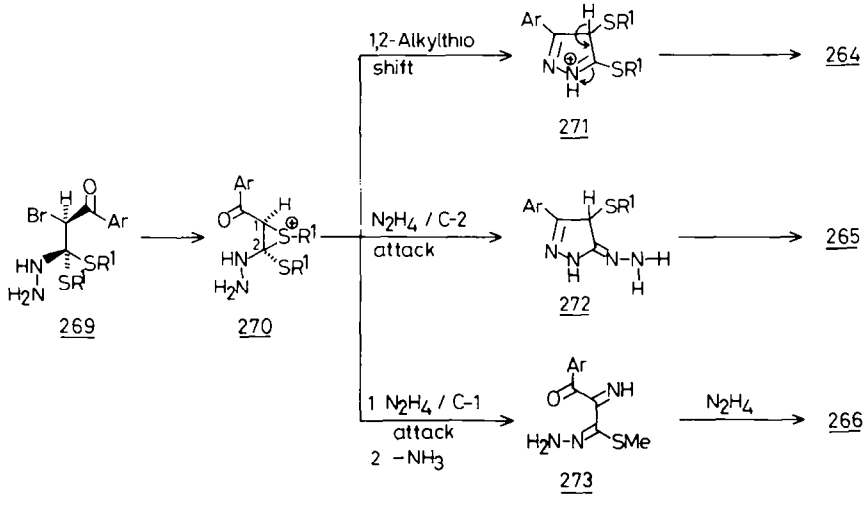
Ar1	Ar2	% yield 262	% yield 263
C_6H_5	C_6H_5	50	50
C_6H_5	4-MeC_6H_4	88	48
C_6H_5	3-MeC_6H_4	83	41
4-MeC_6H_4	3-MeC_6H_4	81	43
4-ClC_6H_4	C_6H_5	–	46
4-$MeOC_6H_4$	C_6H_5	87	–

Scheme 49.



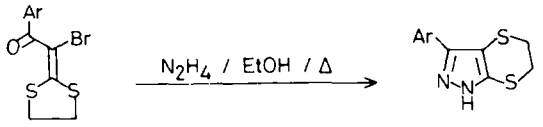
(57)

Ar	R^1	% yield	% yield	% yield
C_6H_5	Me	42	10	30
4-ClC_6H_4	Me	38	8	31
4-MeC_6H_4	Me	41	10	32
C_6H_5	Et	42	–	35



Scheme 50.

concurrent cyclisation affords the 4,5-bis(alkylthio)-pyrazoles **264** (Scheme 50). The other pyrazoles **265** and **266** are also derived from **270** through the attack of a second molecule of hydrazine hydrate either on C-2 or on C-1 respectively. Subsequent events involve either reductive elimination of the methylthio group and molecular nitrogen to give **265** or elimination of ammonia and methylthio group to afford the imine intermediate **273**, which on further reduction with hydrazine hydrate and subsequent cyclisation yields the pyrazole **266** (Scheme 50). The cyclic bromoketene dithioacetals **267** on the other hand react with hydrazine hydrate to yield only 1,4-dithiinopyrazoles **268** exclusively in good yields (eq. 58).[169] The absence of any other rearranged pyrazoles in this reaction suggests



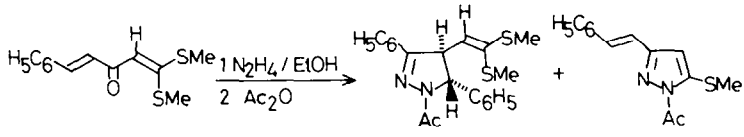
267

268, Ar = C_6H_5, 76%
Ar = 4-ClC_6H_4, 80%
Ar = 4-$MeOC_6H_4$, 62%

(58)

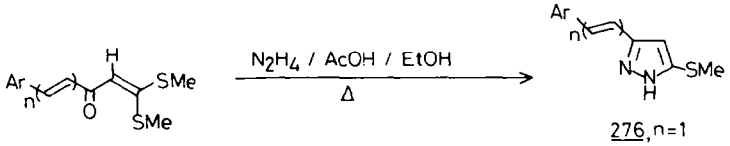
that the formation of **268** does not involve the strained bicyclic episulphonium ion intermediate and instead, appears to proceed by concerted 1,2-alkylthio migration followed by elimination of bromine. When the cinnamoylketene dithioacetal was reacted with hydrazine hydrate in refluxing ethanol, product analysis revealed that ring closure involves the participation of either the styryl double bond or the bis(methylthio) methylene functionality to afford either pyrazoline **274** (after acetylation) or styrylpyrazole **275** respectively (eq. 59).[170]

However, when hydrazine hydrate and cinnamoylketene dithioacetals were reacted in the presence of boiling ethanolic acetic acid, cyclisation takes place involving the bis(methylthio) methylene double bond rather than the styryl double bond to yield only one regioisomeric pyrazoles **276** (eq. 60).[170] Apparently the cationic centre in the protonated carbonyl oxygen in these dithioacetals is better stabilised on the β-bis(methylthio) carbon thereby facilitating the attack of N_2H_4 nitrogen at



274, 68% 275, 21%

(59)



276, n = 1
277, n = 2
278, n = 3

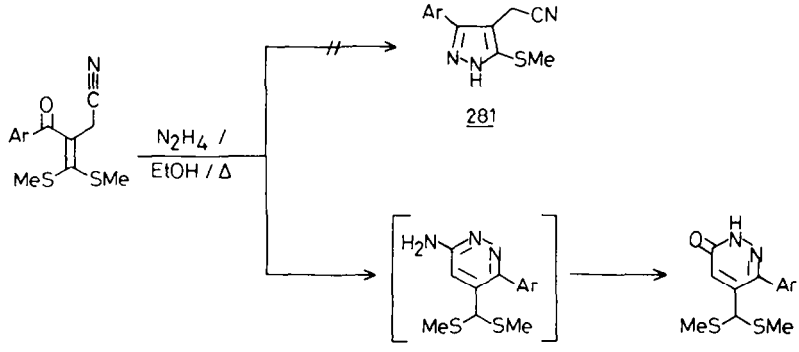
(60)

276, Ar = C_6H_5; 4-$MeOC_6H_4$; 4-ClC_6H_4; 4-$Me_2NC_6H_4$;
2-ClC_6H_4; 2,6-$Cl_2C_6H_3$; 3,4-$(MeO)_2C_6H_3$,
3,4,5-$(MeO)_3C_6H_2$; 3,4-methylenedioxyC_6H_2; 63-80%

277–278 Ar = C_6H_5; 4-$MeOC_6H_4$;
Ar = 3,4-methylenedioxyC_6H_3; 71–77%

that carbon followed by an elimination–cyclisation sequence to afford pyrazoles **276** in good yields. The higher homologous enylpyrazoles **277** ($n = 2$) and **278** ($n = 3$) were also similarly obtained from the reaction of appropriate oxoketene dithioacetals and hydrazine hydrate (eq. 60).[170] The high chemoselectivity of cinnamoylketene dithioacetals towards hydrazine hydrate in the presence of an acidic medium can be attributed to hard–soft dissymmetry of charge and consequent affinity inversion that results in product regioselectivity.

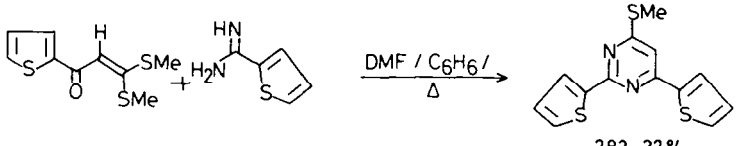
Interestingly, the reaction of hydrazine hydrate and oxoketene dithioacetals derived from β-arylpropionitrile affords the pyridazinones **280** instead of pyrazoles **281** (Scheme 51) through cyclocondensation involving carbonyl and nitrile group followed by *in situ* hydrolysis of the initially formed 2-aminopyridazines **279**.[171]



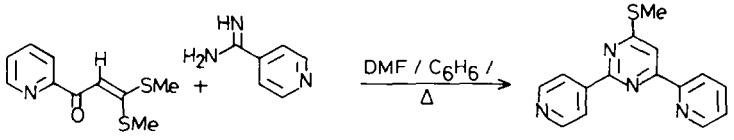
Ar = C_6H_5, 4-ClC_6H_4; 4-MeC_6H_4
4-$MeOC_6H_4$; 4-BrC_6H_4 63-68 %

Scheme 51.

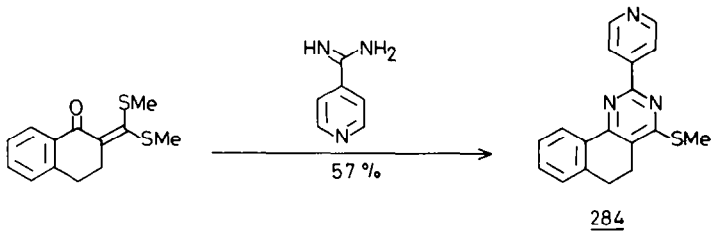
Junjappa and co-workers developed a new general method for the synthesis of 6-alkoxypyrimidines by reacting guanidine with α-oxoketene dithioacetals in the presence of the corresponding alkanol alkoxide medium and proposed that the guanidine reacts with the α-oxoketene O,S-acetals formed *in situ* by displacement of methylthio group of alkoxide ion.[8] In the absence of protic solvents, guanidine reacted with oxoketene dithioacetals to afford 6-alkylthiopyrimidines.[8] This one pot 6-alkoxy and alkylthiopyrimidine synthesis has been discussed in detail in the earlier review. The method is extended by Potts and co-workers for the synthesis of a variety of 2,6-disubstituted-6-methylthio and annelated pyrimidines containing heteroaryl substituents in the 2,6-positions (eq. 61–63).[172] The reaction of bis-(α-oxoketene dithioacetals) **285** with two equivalents of carbox-



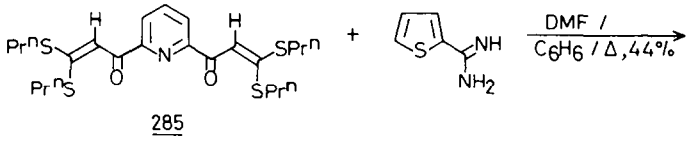
(61)



(62)



284 (63)



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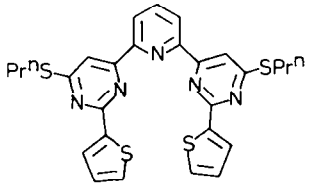
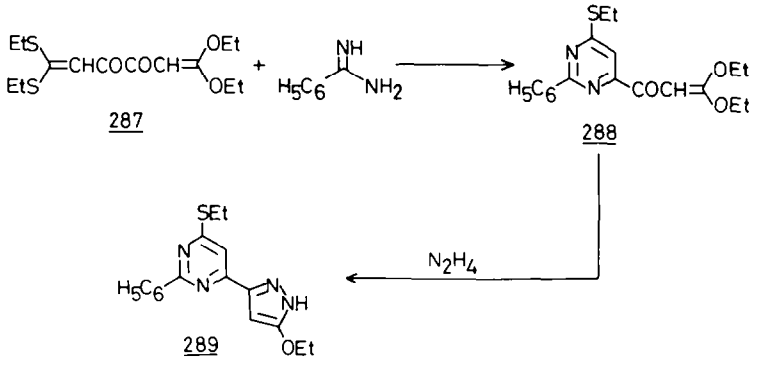


286 (64)

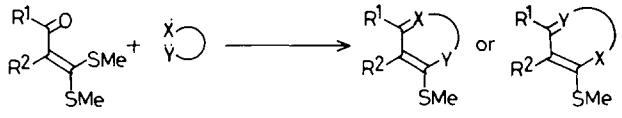
amidines allowed the construction of several pyrimidine nuclei into a polyheteryl system **286** (eq. 64). Interestingly, the bis(α-oxoketene S,S- O,O-acetal) **287** reacts sequentially first with one equivalent of benzimidine to give pyrimidine **288** and then with hydrazine hydrate to afford 4-pyrazolylpyrimidine **289** (Scheme 52).[173]



287 288 289

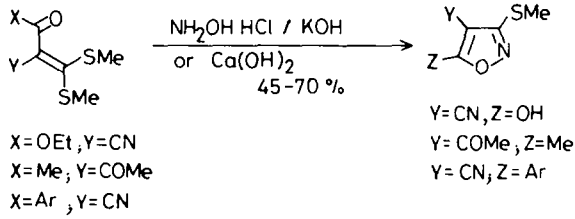
Scheme 52.

The reaction of asymmetric bifunctional heteronucleophiles with α-oxoketene dithioacetals can yield two regioisomeric heterocycles (eq. 65) depending on the electrophilicities of 1,3-carbon centres



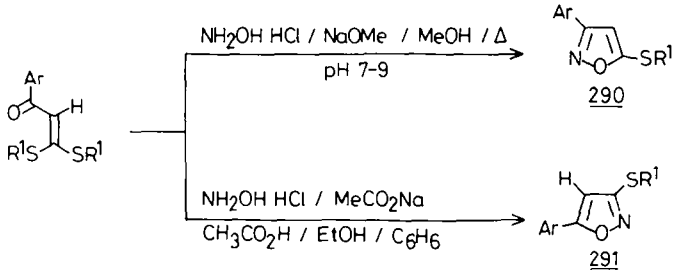
(65)

of the dithioacetals, the nucleophilicities of the heteroatoms in the bifunctional nucleophiles and the reaction conditions (pH of the reaction medium, etc). Evidently, the doubly activated oxoketene dithioacetals are known to react with hydroxylamine to give only the corresponding 3-methylthio-isoxazoles instead of 5-methylthio regioisomers (eq. 66).[162,162d] Apparently, the observed regio-



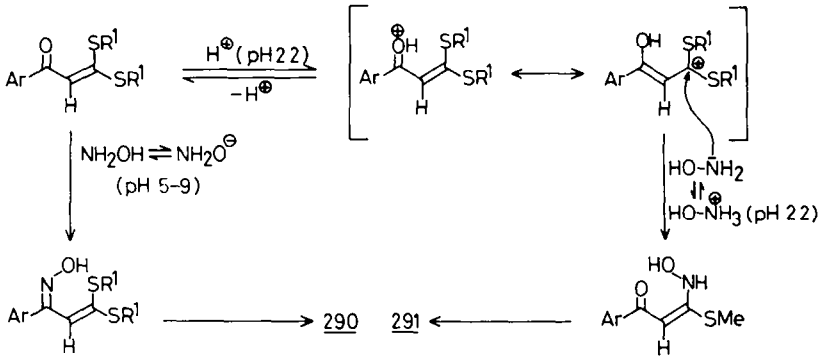
(66)

selectivity emanates from the enhanced polarity of the bis(alkylthio) double bond due to two electron withdrawing α-substituents and consequently the β-carbon with increased electrophilicity is preferentially attacked by the stronger nucleophilic N atom of the hydroxylamine. Junjappa and Ila[174] have investigated in detail the reaction of hydroxylamine with α-oxoketene dithioacetals using different reaction conditions to afford highly regioselective 3- or 5-alkylthioisoxazoles in high yields (Scheme 53). Thus regioselective formation of 5-alkylthioisoxazoles **290** is achieved by using barium hydroxide or sodium methoxide both in equivalent or excess amounts in the pH range 5–9. The predominant species up to pH 10 has been shown to be the neutral hydroxylamine molecule[175] which proves that the role of the base in these reactions is limited to the release of free H_2NOH



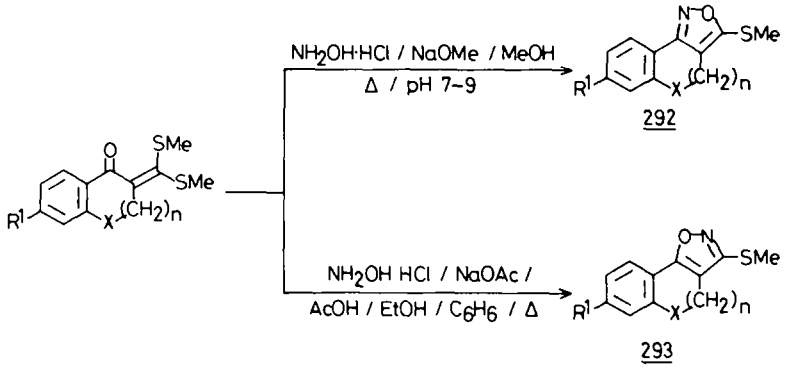
Ar	R^1	% yield 290	% yield 291	Ar	R^1	% yield 290	% yield 291
C_6H_5	Me	78	65	β-naphthyl	Me	68	66
4-MeC_6H_4	Me	77	68	4-pyridyl	Me	68	51
4-ClC_6H_4	Me	71	62	2-furyl	Me	63	68
4-$MeOC_6H_4$	Me	72	63	C_6H_5	Et	58	63
4-BrC_6H_4	Me	71	63	C_6H_5	n-Pr	61	64
2,4-$Cl_2C_6H_3$	Me	70	58				

Scheme 53.



Scheme 54.

from its salt and it does not exert an effect on oxoketene dithioacetals. The course of attack of H_2NOH on oxoketene dithioacetal under these conditions therefore follows the oxime pathway to yield exclusively **290** (Scheme 54). On the other hand, in the presence of sodium acetate/acetic acid (pH 2.2), the dominant species is the hydroxylammonium ion with only a small amount of hydroxylamine being present, which attacks the more electrophilic C-3 of protonated dithioacetal (HSAB) (hard–soft dissymmetry) in the rate-determining step. Cyclisation then follows to yield the 3-alkylthioisoxazoles **291**, while the hydroxylamine is regenerated in the equilibrium mixture (Scheme 54).[174] The cyclic oxoketene dithioacetals, under identical conditions, afford the regioisomeric condensed isoxazoles **292** and **293** in good yields (eq. 67 and 68). In summary, the isomeric 5-

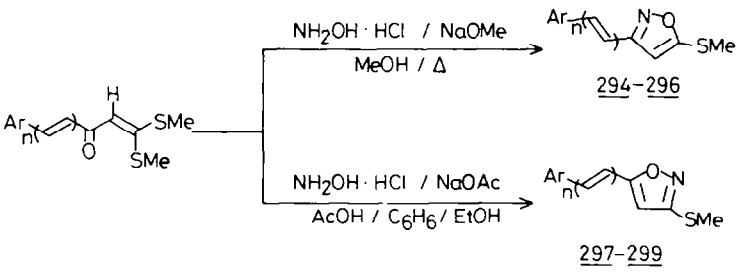


(67)

(68)

R^1	X	n	% yield 292	% yield 293
H	CH_2	1	78	64
MeO	CH_2	1	57	53
Me	S	2	78	53

alkylthio or 3-alkylthioisoxazoles can be obtained at will from the same starting reactants by simply using the appropriate reaction conditions. The reaction could also be extended to cinnamoylketene dithioacetals and their higher enyl homologs to afford the expected regioisomers **294–296** and **297–299** under the described conditions (eq. 69 and 70).[170]

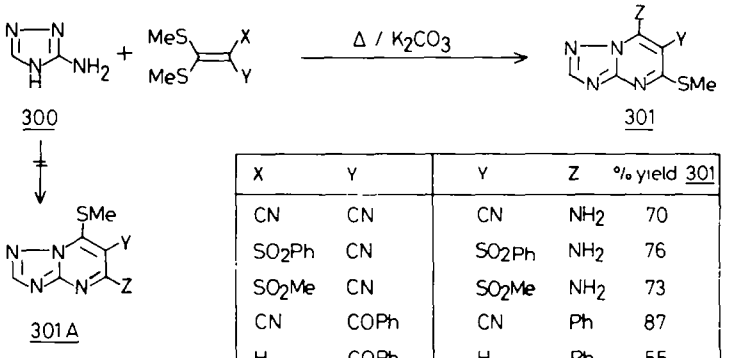


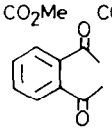
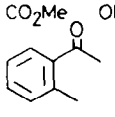
294,297, n=1; Ar= C_6H_5; 4-MeC_6H_4; 4-ClC_6H_4; 4-MeOC_6H_4; 4-$Me_2NC_6H_4$; 3,4-methylenedioxyC_6H_3, 2-ClC_6H_4; 2,6-$Cl_2C_6H_3$, 2,4-$Cl_2C_6H_3$; 35–65 %

295,298, n=2, Ar= C_6H_5, 4-MeOC_6H_4, 3,4-methylenedioxyC_6H_3; 58–66 %

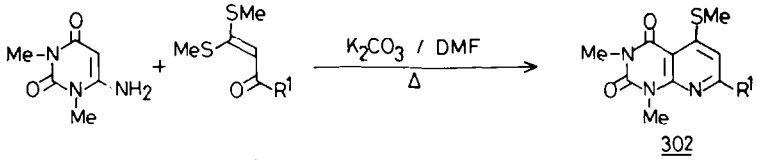
296,299, n=3; Ar= C_6H_5, 4-MeOC_6H_4; 3,4-methylenedioxyC_6H_3; 47–59 %

Tominaga and co-workers[176] have reacted a few cyano and oxoketene dithioacetals with 3-aminotriazoles as an amidine functionality either under direct thermal conditions or in the presence of potassium carbonate to afford triazolo[1,5-*a*]pyrimidines **301** in good yields (Scheme 55). The formation of **301** can be explained by an initial conjugate -addition sequence followed by cyclisation. However, no attempts were made to study whether the regioisomeric triazolopyrimidines **301A** could be isolated under varying conditions. The same authors have also reacted 6-aminouracil derivatives as an enaminone functionality with oxoketene dithioacetals, in the presence of K_2CO_3, to afford pyrido[2,3-*d*]pyrimidines (eq. 71, 72).[177] Interestingly the *β*-enamino carbon of uracil, a soft nucleophile, is expected to be the attacking species on the *β*-carbon (soft electrophile) of the oxoketene dithioacetals and is followed by cyclisation to afford **302** and **303** (eq. 71, 72).[177] Junjappa and Ila[178] have also studied the reaction of unsubstituted 6-aminouracil with cyclic ketene



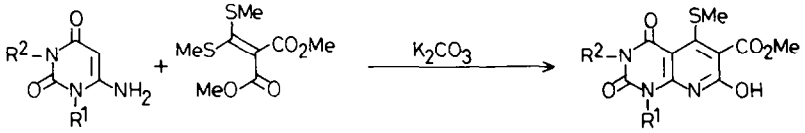
X	Y	Y	Z	% yield 301
CN	CN	CN	NH_2	70
SO_2Ph	CN	SO_2Ph	NH_2	76
SO_2Me	CN	SO_2Me	NH_2	73
CN	COPh	CN	Ph	87
H	COPh	H	Ph	55
CN	CO_2Me	CN	OH	32
CO_2Me	CO_2Me	CO_2Me	OH	57
				85

Scheme 55.



(71)

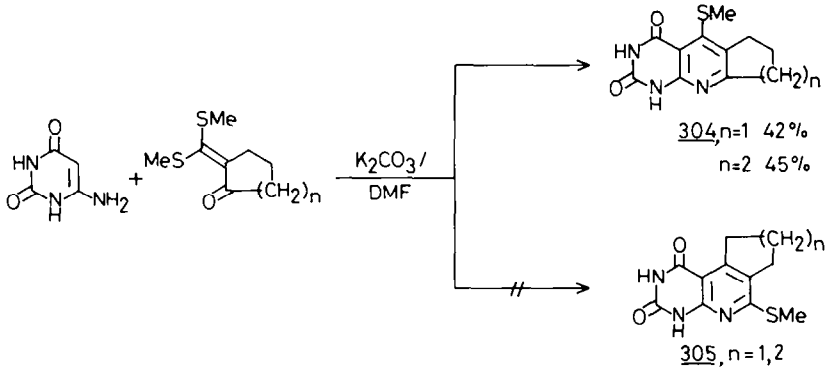
R^1 = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4; 2-furyl, 40-85%



(72)

dithioacetals to afford linear pyridopyrimidines **304** (eq. 73) and attempted isolation of angular derivatives **305** under varying conditions was not successful (eq. 73).

Gompper and Topfl[163a] have similarly reported the formation of pyrazolopyridone **306** by reacting 3-amino-4-hydroxy pyrazole with doubly activated oxoketene dithioacetal, where the carbon nucleophile (SN) of the enol rather than the nitrogen nucleophile of the amidine functionality is the attacking atom on the β-carbon of the acetal (eq. 75). These observations warrant further



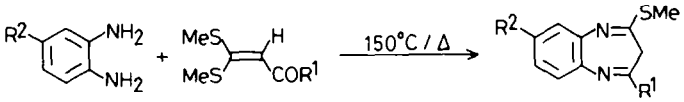
(73)

(74)

(75)

investigation especially under HSAB affinity inversion to examine whether it is possible to create the conditions necessary to direct the course of reaction that may lead to different regioisomers. Kobayashi and co-workers[179] have reacted *o*-phenylenediamine with α-oxoketene dithioacetals to

afford 8-substituted 4-aryl-2-methylthio-1,5-benzodiazepine **307** regioselectively in moderate to good yields (eq. 76). Similarly the corresponding thienodiazepine derivatives **309** and **310** were obtained

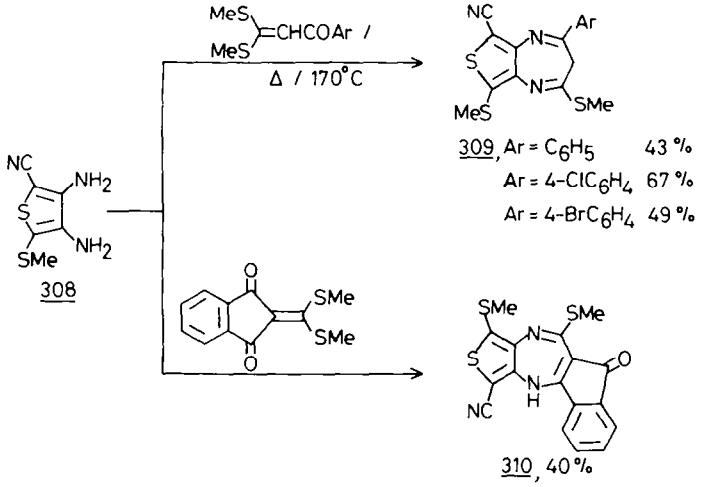


(76)

307

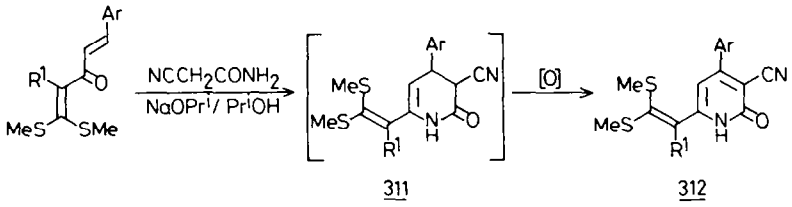
R^1	R^2	% yield
C_6H_5	NO_2	55
4-ClC_6H_4	NO_2	73
4-BrC_6H_4	NO_2	78
4-ClC_6H_4	Cl	56
2-thienyl	NO_2	97

by condensation of 5-substituted-3,4-diaminothiophenes with oxoketene dithioacetals[180] (Scheme 56). The regioselectivity in these reactions is controlled by the electron-withdrawing nitro and cyano groups on the diamines.



Scheme 56.

The cyclocondensation of enolate anion of cyanoacetamide with oxoketene dithioacetals is shown to proceed by initial 1,4-conjugate addition of carbanion followed by intramolecular attack of amide nitrogen on the carbonyl carbon to afford 3-cyano-4-alkylthio-5,6-substituted-2(1H)-pyridones.[164] These reactions have been extensively investigated and are covered in the earlier review. The cyanocetamide anion was then reacted with cinnamoyl ketene dithioacetals which possess ambident 1,3-electrophilic centres that might compete with cyanoacetamide anion to give different products.[181] The pyridones **312** were formed predominantly by air oxidation of the initially formed intermediate **311**, without the participation of the mercapto functionality, while those with bis(methylthio) double bond participation were few and obtained in low yields (eq. 77). The



(77)

311 312

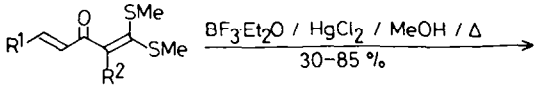
Ar=C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, $C_6H_5CH{=}CH{-}$; R^1=H; 73–88 %

Ar=4-ClC_6H_4; R^1=Me; 77 %

reactivity pattern of the cyanoacetamide anion with these dithioacetals could not be rationalised in terms of both steric and electronic considerations.

7. MISCELLANEOUS REACTIONS

There are many reactions of α-oxoketene dithioacetals that do not fall into the categories of the reactions described above. The dithioacetal functionality in these systems can be considered as a latent ester group since it could eventually be converted to the corresponding ester group Lewis-acid assisted solvolysis. The corresponding thiolesters can also be obtained under Lewis acid assisted hydrolytic conditions.[7] When cinnamoylketene dithioacetals were treated under solvolytic conditions with a methanolic mixture of $BF_3 \cdot Et_2O/HgCl_2$(1 : 1) the corresponding γ,δ-unsaturated-β-ketoesters **313** were obtained in excellent yields (eq. 78).[182] However, the 2,4-dimethylcinnamoyl



30–85 %

(78)

313 A 313 B

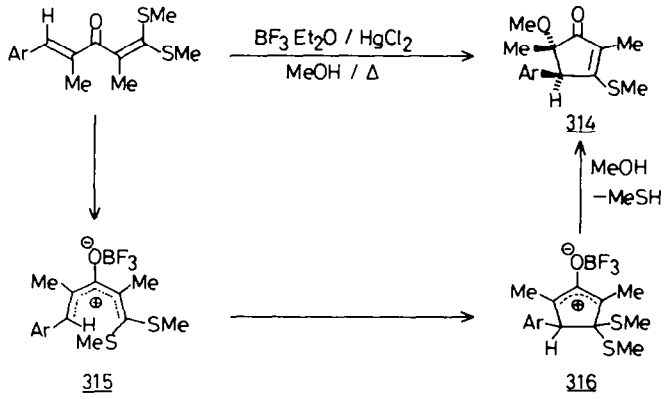
R^1=C_6H_5; 4-MeC_6H_4; 4-ClC_6H_4; 4-$MeOC_6H_4$; 3,4-$(MeO)_2C_6H_3$; 3,4,5-$(MeO)_3C_6H_2$; 3,4-methylenedioxyC_6H_3; R^2= H; 64–72 %

R^1=$C_6H_5CH{=}CH{-}$; R^2=H, 30 %

R^1=C_6H_5; 4-ClC_6H_4, 4-$MeOC_6H_4$; R^2=Me; 83–85 %

ketene dithioacetals, when heated under the above solvolytic conditions, gave the corresponding cyclopentenones **314** instead of **313** (Scheme 57).[182] The mechanism governing these transformations involving symmetry-allowed Nazarov-type ring closure has been discussed in section 4.

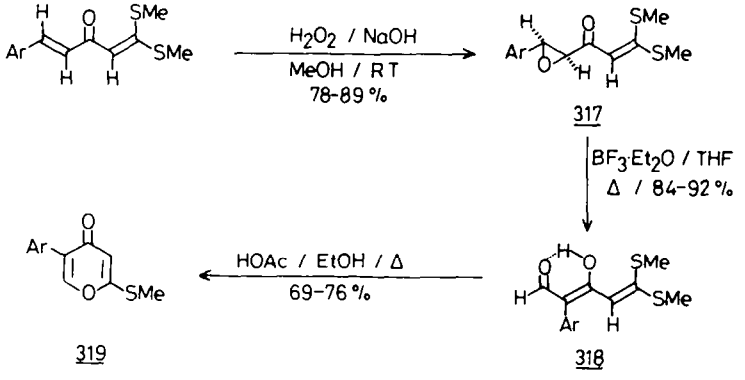
The chemoselective epoxidation of styryl double bond, in cinnamoylketene dithioacetals, was achieved with alkaline H_2O_2 to afford the corresponding epoxyketones **317** in high yields.[182] These epoxyketones **317** underwent BF_3 ether assisted rearrangements first to the β-ketoaldehydes **318** and then cyclised to afford 2-methylthio-5-arylpyran-4-ones **319** on heating with ethanolic acetic



314 Ar = C_6H_5, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-$MeOC_6H_4$, 3,4-methylenedioxyC_6H_3; 55–73 %

Scheme 57.

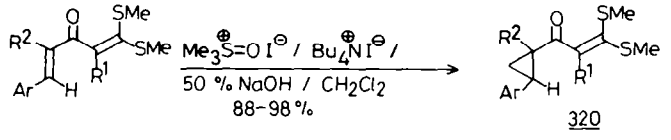
acid (Scheme 58).[183] Similarly the styryl double bond in these acetals, when treated with dimethylsulphoxonium methylide under phase transfer conditions, underwent cyclopropanation to yield the corresponding cyclopropylketones **320** in excellent yields (eq. 79).[184] These cyclopropyl ketones



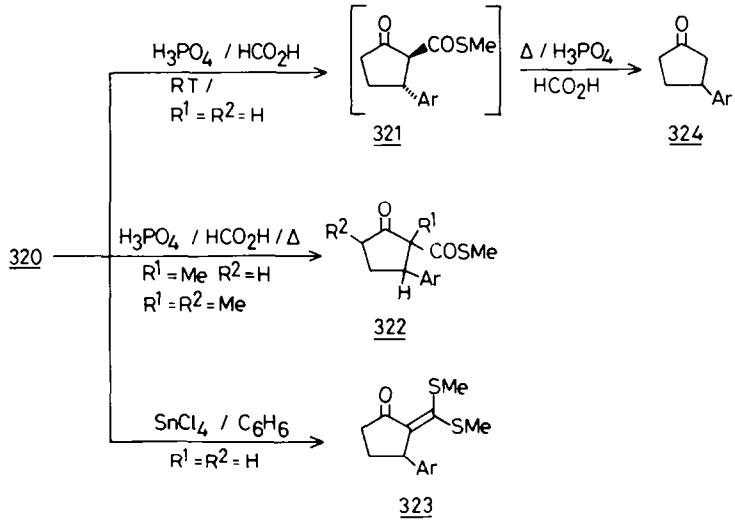
317–319 Ar = C_6H_5, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 3,4,5-$(MeO)_3C_6H_2$, 3,4-methylenedioxyC_6H_3

Scheme 58.

were of particular interest for acid-catalysed rearrangement studies since the bis(methylthio)-methylene double bond would participate intramolecularly with the developing carbocation during acid-assisted ring opening of the cyclopropane with the formation of a new C–C bond leading to cyclopentanones (Scheme 60).



(79)

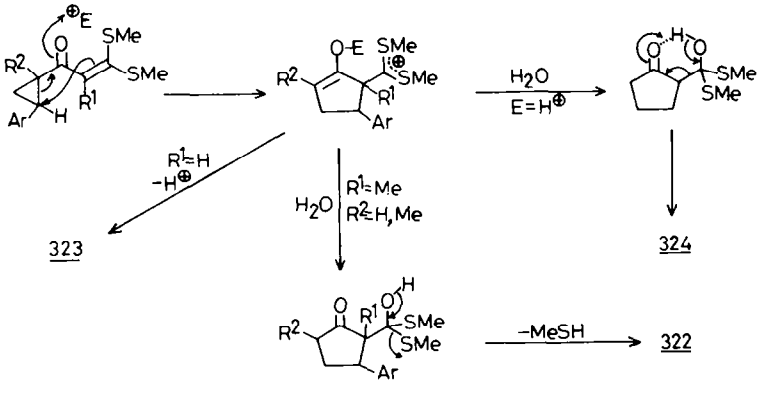


320-324, Ar= 4-MeOC$_6$H$_4$; 3,4-(MeO)$_2$C$_6$H$_3$; 3,4,5-(MeO)$_3$C$_6$H$_2$; 3,4-methylenedioxyC$_6$H$_3$ 68–80%

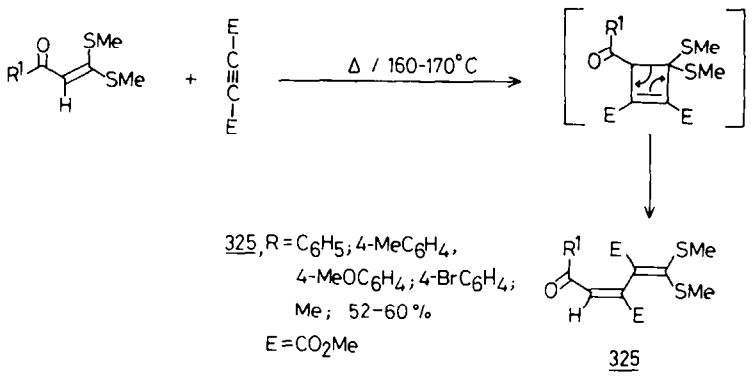
324, Ar=4-MeC$_6$H$_4$ 37%

Scheme 59.

The envisaged cyclopentanones **321** and **322** (H_3PO_4/HCO_2H), **323** ($SnCl_4/C_6H_6$) were indeed formed under varying acidic conditions (Scheme 59).[184] The three-membered ring opening and cyclisation through π-participation leading to cyclopentanones has successfully circumvented the limitations observed in the corresponding β-ketoesters which undergo intramolecular O-alkylation to furans rather than intramolecular C-alkylation.[185] Thus the transformation constitutes a novel intramolecular alkylation approach to substituted cyclopentanones. However, the method was successful only with cyclopropyl ketones having aryl groups with electron-donating substituents. The acyclic oxoketene dithioacetals react with dimethylacetylene dicarboxylate in the [2+2] fashion to mercapto double bond to afford cyclobutene intermediates followed by ring opening to the

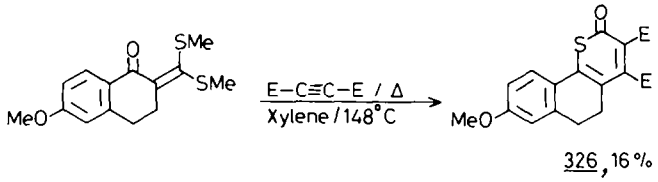


Scheme 60.



Scheme 61.

corresponding dienes **325** (Scheme 61).[186] On the other hand, the cyclic oxoketene dithioacetal derived from 6-methoxytetralone reacts with DMAD to give the fused thiopyrone derivative **326** (eq. 80) in low yield.[186] The formation of **326** has been rationalised through an interesting sequence



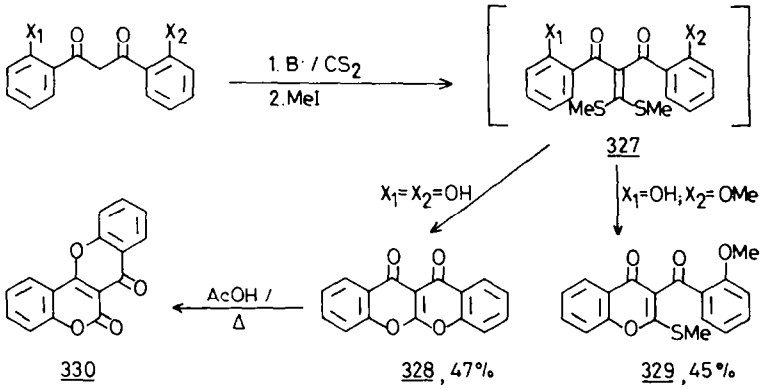
(80)

of rearrangements involving initial [2+2] cycloaddition, ring opening and electrocyclisation of the diene followed by an intramolecular 1,5-sigmatropic shift of the methylthio group.[186]

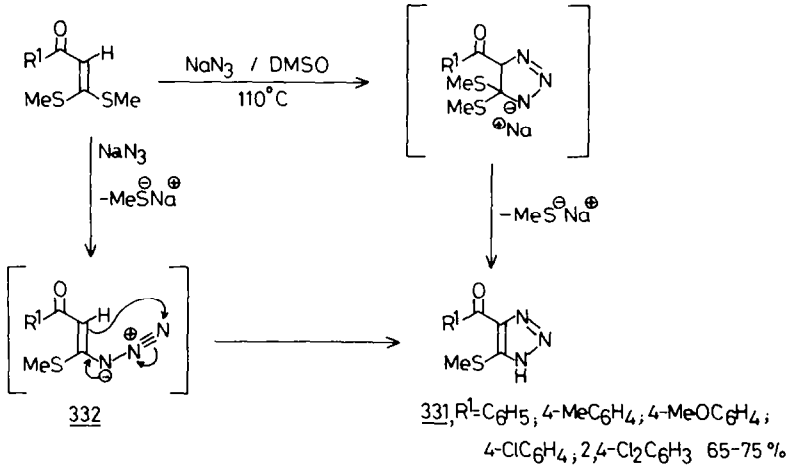
The intermediacy of α-oxoketene O,S-acetals was first demonstrated by Junjappa and Chauhan[8] in the conversion of α-oxoketene dithioacetals into alkoxypyrimidines and alkoxypyrazoles although the isolation of these systems was never achieved by direct displacement of thiomethyl group by alkoxide ion. However, recently an interesting example of thiomethyl displacement by alkoxy group was achieved in the corresponding sulphonium salts of oxoketene dithioacetals to give the O,S-acetals in good yields.[187] Thus the chemistry of oxoketene O,S-acetals has remained yet unexplored, although most of the reactions studied for S,S-acetals could well be extended to these systems to yield the corresponding alkoxy instead of thiomethyl end products.

Eiden and Schweiger[188] have shown that the dithioacetals **327** derived from *o*-hydroxydibenzoylmethanes undergo *in situ* cyclisation to bispyrone **328** and pyrone **329** through intramolecular displacement of thiomethyl group by phenoxide ion (Scheme 62).

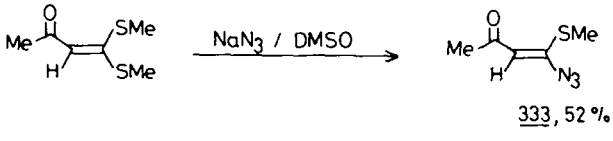
The α-oxoketene dithioacetal double bond is reported to function as a good dipolarophile in the 1,3-dipolar cycloaddition reactions with sodium azide to afford 4-aroyl-5-methylthiotriazoles **331** through elimination of methylmercaptan from triazoline intermediates (Scheme 63).[189] The corresponding dithioacetal derived from acetone, however, yielded only the unstable β-azidoketone **333** under identical conditions (eq. 81). The 1,3-dipolar cycloadditions were, however, not successful with benzonitrile oxide or diphenylnitrileimines which gave only oxoketene dithioacetals back. These findings demand further investigation on the mechanism of triazole formation through azide reaction. Thus alternatively, the triazoles **331** may arise through electrocyclisation of β-azidoketones **332** formed by displacement of methylmercapto group by an azide anion (Scheme 63).



Scheme 62.



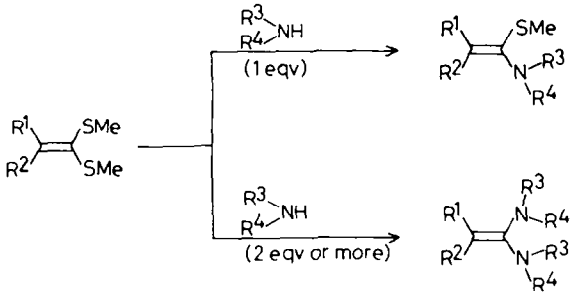
Scheme 63.



(81)

8. OXOKETENE N,S- AND N,N-ACETALS

The doubly activated ketene dithioacetals undergo an addition elimination sequence with primary and secondary amines to yield the corresponding N,S- and N,N-acetals in high yields.[1b,58,64] In these systems, the formation of N,S- and N,N-acetals can be controlled by the stoichiometry of the added amines. On the other hand, the less reactive α-oxoketene dithioacetals require more vigorous conditions and generally afford a mixture of N,S- and N,N-acetals.[190,165a,17] Therefore an alternative convenient method of preparation of N,S-acetals involves the reaction of enolate anion with isothiocyanates followed by alkylation.[15,161,23,24,189,190] These and other methods[191,192] employed (eq. 82–90) for the preparation of N,S- and N,N-acetals have been covered in the earlier review.[193,194] The



(82)

(83)

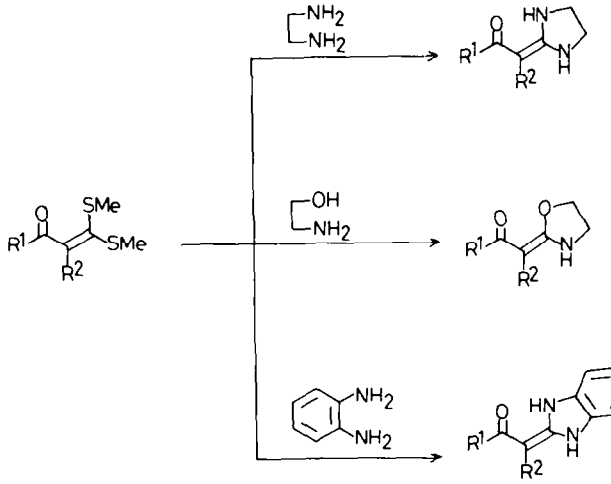
R^1 = CN, R^2 = CN, $CONH_2$, CO_2Alk, R^1 = CO_2Alk, R^2 = CO_2Alk, MeCO, ArCO

R^1 = MeCO, ArCO, R^2 = MeCO, ArCO, CN, SO_2Ar

R^3 = H, R^4 = alkyl, aryl

R^3 = R^4 = morpholino, pyrrolidino, piperidino, aziridino

R^1 = ArCO, MeCO; R^2 = H; R^3 = Aryl, Alkyl; R^4 = H



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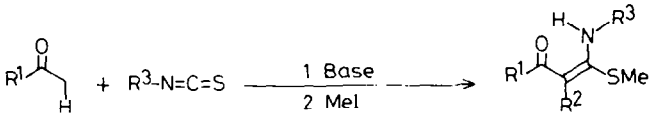
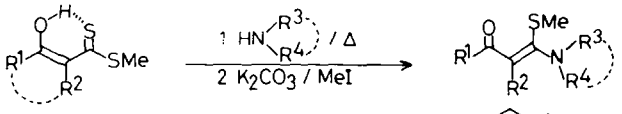
(85)

(86)



(87)

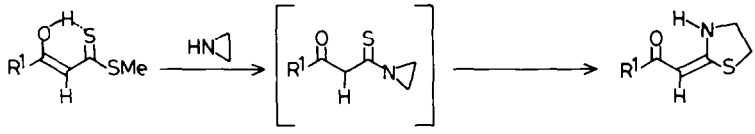
R^1 = substituted aryl, methyl, R^2 = H, R^3 = substituted aryl, Me, Et, n-Pr, i-Pr, n-Bu, CycloC_6H_{11}, $C_6H_5CH_2$



(88)

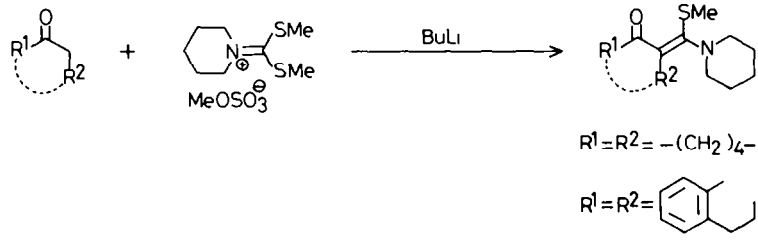
R^1 = Me, substituted aryl; R^2 = H; R^1 = R^2 = $-(CH_2)_4$,

R^3 = R^4 = Me; Et; R^3 = C_6H_5; R^4 = Me; R^3 = R^4 = pyrrolidino, morpholino, N-phenylpiperizino; R^3 = CH_2CO_2Et; R^4 = H



(89)

R^1 = Me, C_6H_5; 4-ClC_6H_4; 4-MeC_6H_4; 4-$MeOC_6H_4$



(90)

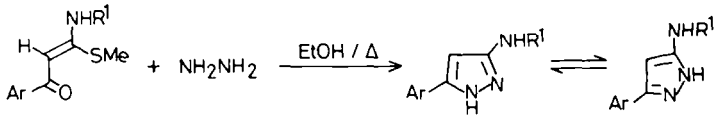
$R^1 = R^2 = -(CH_2)_4-$

reactivity pattern of oxoketene N,S-acetals, like their dithioacetals, can be viewed in several ways. Thus the N,S-acetals undergo cyclocondensation with several bifunctional nucleophiles to give aminoheterocycles by replacement of the methylthio group of N,S-acetals. On the other hand, these intermediates can be viewed as novel functionalised enaminones which react at the β-carbon with several electrophilic species followed by ring closure to a variety of heterocycles. In oxoketene N,S-acetals, the reduced electrophilicity of the carbonyl carbon atom can be attributed to the hard–soft affinity inversion and we expect that the hard nucleophiles generally attack at the β-carbon (HE) atom. On the basis of these reactivities the oxoketene and cyanoketene N,S- and N,N-acetals can be broadly classified into the following categories:

1. Oxoketene and cyanoketene N,S- and N,N-acetals as three-carbon fragments.
2. Oxoketene and cyanoketene N,S- and N,N-acetals as novel functionalised enaminones and enaminonitriles.
3. Miscellaneous reactions.

8.1. *Oxoketene and cyanoketene N,S- and N,N-acetals as three-carbon fragments*

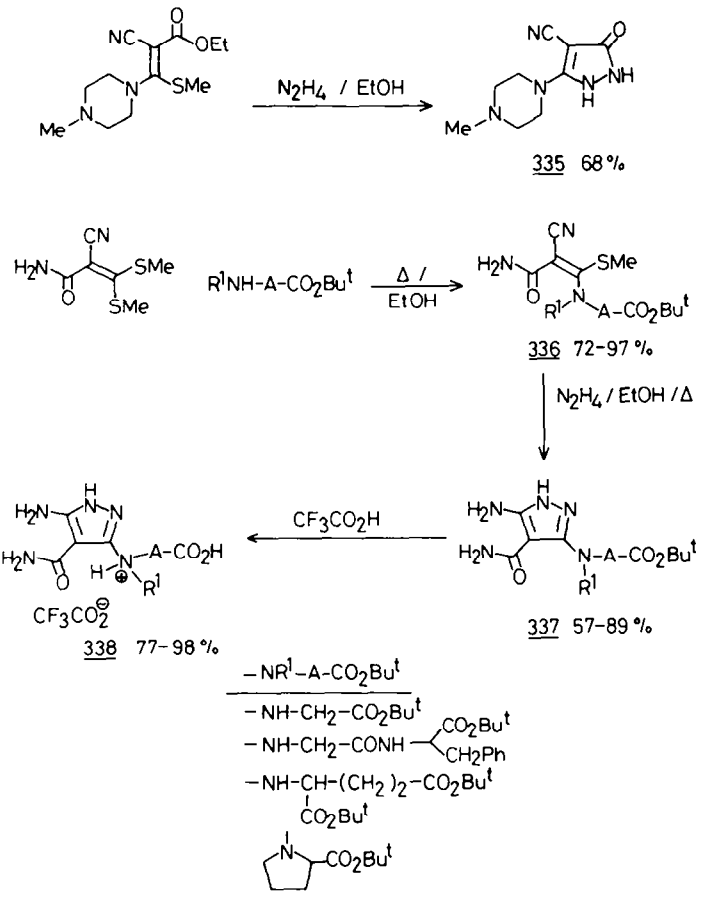
With bifunctional nucleophiles like guanidine,[163c,190,163d,195,196] cyanoacetamide enolate,[197] the oxoketene and cyanoketene N,S-acetals are generally known to yield the corresponding 4-alkyl/arylamino (secondary amino) pyrimidines and 4-aminopyridones respectively. Similarly, the hydroxylamine is known to yield the corresponding 3-aminoisoxazoles,[162d,193,198] a regioisomer which is formed by the attack of the N-nucleophilic centre of the H_2NOH at the β-carbon reminiscent of the hard–soft dissymmetry induced through displacement of MeSH group by nitrogen nucleophile.[198] These reactions have been extended for the synthesis of aryl/alkylamino pyrazoles[162b,162d,199] or aminopyrazolones (eq. 92) by treating oxoketene N,S-acetals with hydrazine



(91)

334 51–97 %

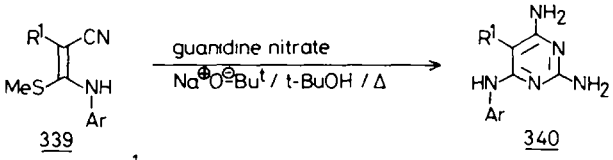
Ar = substituted aryl; R^1 = Me, Et, $C_6H_5CH_2$, substituted aryl



(92)

Scheme 64.

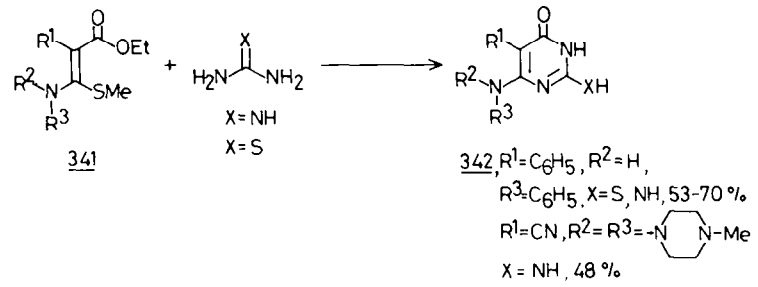
hydrate. Yokoyama and co-workers[200] have recently reported the synthesis of new N-(5-amino-pyrazol-3-yl) derivatives **337** of aminoacids and dipeptides by reacting α-(aminocarbonyl)-α-cyano-ketene dithioacetals with amino acids or *t*-butylesters of dipeptides to afford the intermediate N,S-acetals **336** containing nitrogen as a part of the peptide chain. These N,S-acetals reacted with hydrazine hydrate to afford the pyrazoles which on treatment with trifluoroacetic acid yielded the corresponding trifluoroacetates **338** (Scheme 64). Junjappa, Ila and co-workers[196] have also reacted the α-cyano-N,S-acetals **339** derived from arylacetonitrile, malononitrile and α-carbethoxy N,S-acetals **341** with guanidine or thiourea to give the corresponding 2,4-diamino-6-anilinopyridines **340** and 6-amino-4-oxopyrimidines **342** in good yields (eq. 93, 94).



339 340

(93)

339,340, R^1 = C_6H_5; 4-ClC_6H_4; 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$
Ar = C_6H_5, 69-90%
R^1 = CN, Ar = o-FC_6H_4, 4-ClC_6H_4, 48-52%

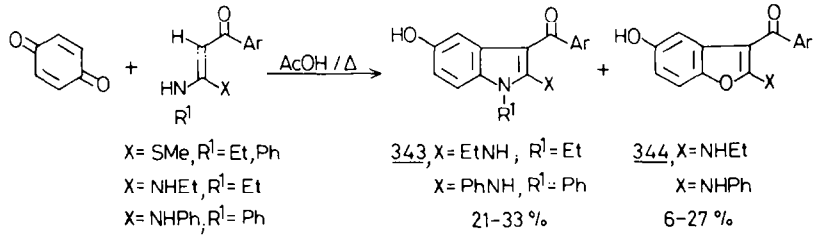


(94)

8.2. *Oxoketene and cyanoketene N,S-acetals as novel functionalised enaminones and enaminonitriles*

The oxo and cyanoketene N, S- and N,N-acetals function as enaminones where the α-position can act as nucleophile and react with electrophilic species resulting in their further functionalisation and finally to a variety of heterocycles. Thus oxoketene N,S-acetals are reported to undergo cyclocondensation with benzoylisothiocyanate to afford 5-aryl-6-methylthio-4-thioxopyridones.[201] Similarly, they react with dimethylacetylene dicarboxylate to afford open-chain enamine adducts, while the adducts from N,N-acetals with DMAD undergo further cyclisation to afford N-aryl-6-anilinopyridones.[202]

Junjappa, Ila and co-workers[203] have utilised these enamines in Nenitzescu indole synthesis to get the corresponding 5-hydroxyindoles. Thus the oxoketene N,S- and N,N-acetals react with 1,4-benzoquinone to yield a mixture of 5-hydroxyindoles **343** and the corresponding benzofurans **344** in varying yields (eq. 95, 96). Similarly the reaction of oxoketene N,S-acetals with maleic anhydride



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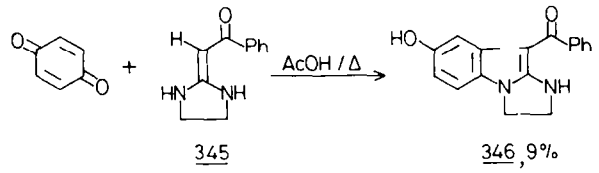
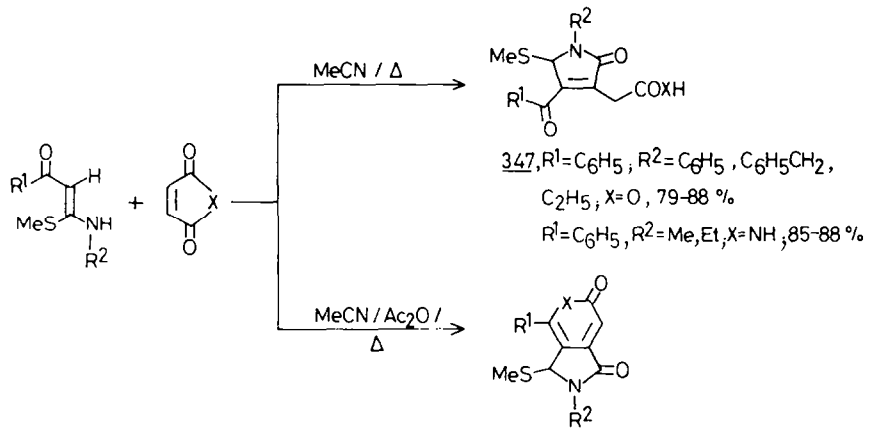


(96)

and maleimide affords the corresponding pyrrolinone-3-acetic acid and amide **347** in excellent yields (Scheme 65).[204] These pyrrolinone-3-acetic acids and the corresponding amides undergo cyclodehydration in the presence of acetic anhydride or by direct heating to afford pyranopyrroles **348** and pyrrolopyridones **349** respectively (Scheme 65). The pyranopyrroles **348** could be obtained in a one-pot reaction by directly heating N,S-acetals and maleic anhydride in acetic anhydride (Scheme 65). The cyclic N,S- and N,N-acetals **350** react with maleic anhydride under identical conditions to afford the corresponding pyrrolothiazolines **351** and pyrroloimidazolines **352** (eq. 97).[204]

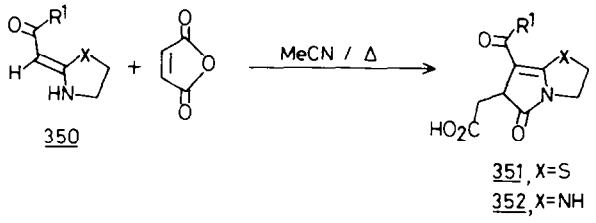


347, $R^1 = C_6H_5$; $R^2 = C_6H_5$, $C_6H_5CH_2$, C_2H_5; X = O, 79–88 %
$R^1 = C_6H_5$, R^2 = Me, Et; X = NH; 85–88 %

348 $R^1 = C_6H_5$, 4-$MeOC_6H_4$, 4-ClC_6H_4; 4-MeC_6H_4, Me
R^2 = Me, Et, $C_6H_5CH_2$, C_6H_5
X = O, 75–88 %

349 $R^1 = C_6H_5$; R^2 = Me, Et; X = NH, 70–82 %

Scheme 65.



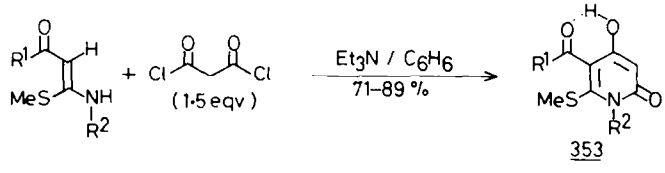
(97)

350

351, X = S
352, X = NH

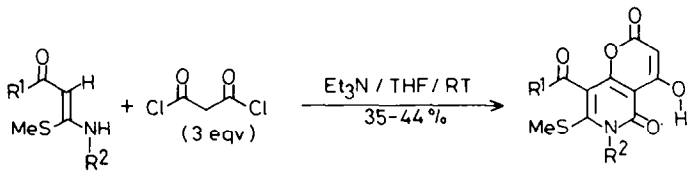
351, R^1 = 4-ClC_6H_4, 4-$MeOC_6H_4$; Me, 85–91 %
352, $R^1 = C_6H_5$; 4-ClC_6H_4; 4-$MeOC_6H_4$; 82–87 %

The oxoketene N,S-acetals are shown to react with malonyl chloride to afford the 4-hydroxy-6-methylthio-2(1H) pyridones **353** in good yields (eq. 98).[205] Interestingly when excess malonyl chloride is used, the reaction further proceeds to yield the corresponding pyranopyridones **354** in moderate yields (eq. 99).[205] Similar cyclisation of oxoketene N,S-acetals with oxalyl chloride affords 4-aryl-5-methylthio-N-substituted pyrroline-2,3-diones **355** in high yields.[206] These pyrrolinediones



(98)

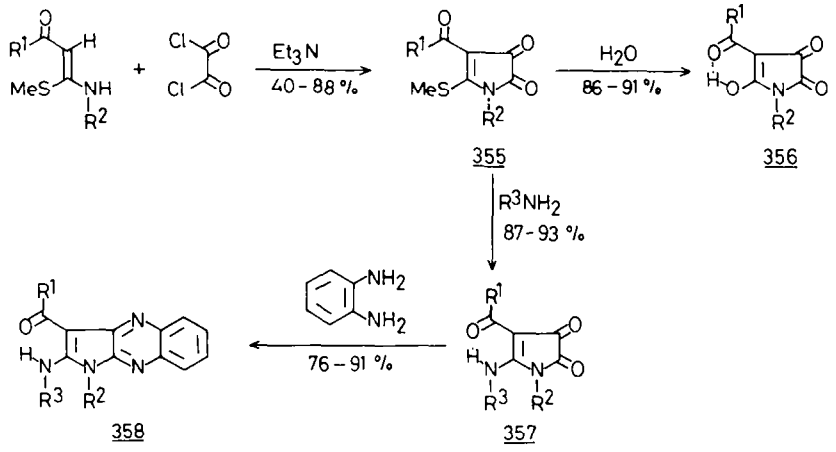
353, $R^1 = C_6H_5$, 4-ClC_6H_4, 4-$MeOC_6H_4$, Me
$R^2 = C_6H_5$; 4-MeC_6H_4; Me; Et, n-Pr, n-Bu; CycloC_6H_{11}, $C_6H_5CH_2$



(99)

354, $R^1 = C_6H_5$, Me; R^2 = Me, Et, $C_6H_5CH_2$

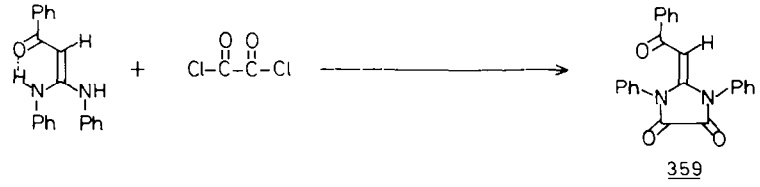
undergo facile displacement of MeSH group by amines or water to give the corresponding 5-amino (**357**) and 5-hydroxy (**356**) derivatives respectively. Some of the 5-aminopyrroline-2,3-diones have been shown to react with *o*-phenylenediamine to afford pyrroloquinoxalines **358** in good yields (Scheme 66).[206] On the other hand the ketene N,N-acetals derived from primary amines react with oxalyl chloride to afford imidazolinediones **359** (eq. 100).[206]



355-358 $R^1 = C_6H_5$, 4-MeC_6H_4; 4-$MeOC_6H_4$; 4-BrC_6H_4; 4-ClC_6H_4

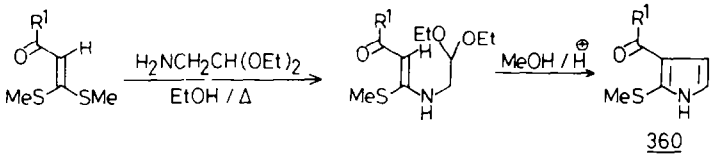
$R^2, R^3 = C_6H_5$; 4-ClC_6H_4; 4-MeC_6H_4; $C_6H_5CH_2$; C_2H_5

Scheme 66.



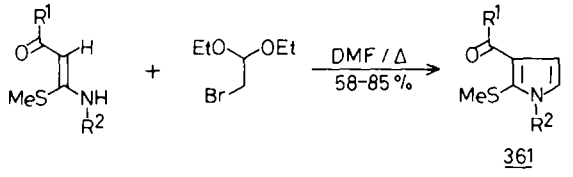
(100)

The N,S-acetals derived from oxoketene dithioacetals and aminoacetaldehyde diethylacetal, an interesting nucleophile with a terminal electrophilic diethylacetal carbon atom, undergo acid catalysed cyclisation to afford 2-methylthio-3-acyl pyrroles **360** in good yields (eq. 101).[207] The method could not be extended to N-substituted pyrroles since the displacement of thiomethyl groups by N-substituted aminoacetaldehyde diethylacetal gave poor yields of the corresponding N,S-acetals. This limitation was circumvented by reacting the appropriate oxoketene N,S-acetals with bromoacetaldehyde diethylacetal in hot DMF to afford N-substituted pyrroles **361** in good yields (eq. 102).[208] The cyclic N,S-acetals under similar reaction conditions afforded the corresponding pyrrolothiazolines **362** (eq. 90).[208]



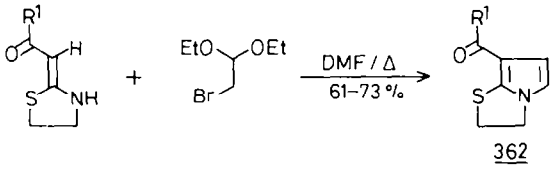
(101)

360, R^1 = Me, 4-MeC_6H_4, C_6H_5, 4-$MeOC_6H_4$, 4-ClC_6H_4; 52–66 %



(102)

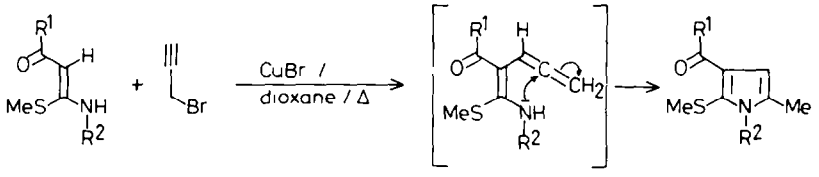
361, R^1 = Me, C_6H_5, 4-ClC_6H_4
R^2 = Me, Et, n-Pr, n-Bu, C_6H_5, $C_6H_5CH_2$



(103)

362 R^1 = Me, C_6H_5, 4-ClC_6H_4

The N,S-propargyl acetals (from secondary amines) under thermal conditions afforded the corresponding N-(azacycloalkyl)-3-acyl-4-methylthiophenes[209] while the corresponding N,S-propargylacetals derived from primary amines underwent *in situ* cyclisation on the triple bond to afford the corresponding N-substituted thiazoline derivative.[210] This strategy was also extended to pyrrole synthesis. Thus the N,S-acetals and propargyl bromide react in the presence of Cu(I) bromide to afford 3-acyl-5-methyl-2-methylthiopyrroles **364** in good yields (eq. 104, 105).[211] The

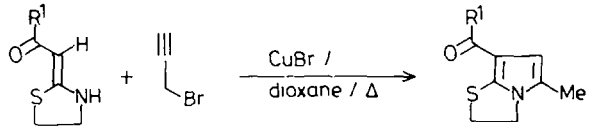


(104)

364 R^1 = Me; C_6H_5, 4-ClC_6H_4; 4-MeC_6H_4
R^2 = Me, Et, n-Pr, i-Pr, n-Bu, C_6H_5, $C_6H_5CH_2$; cycloC_6H_{11}, 48–79 %

pyrroles **364** are presumably formed by intramolecular cyclisation of the allene intermediate **363** formed by nucleophilic attack on the triple bond followed by allylic elimination of HBr (eq. 104).[211]

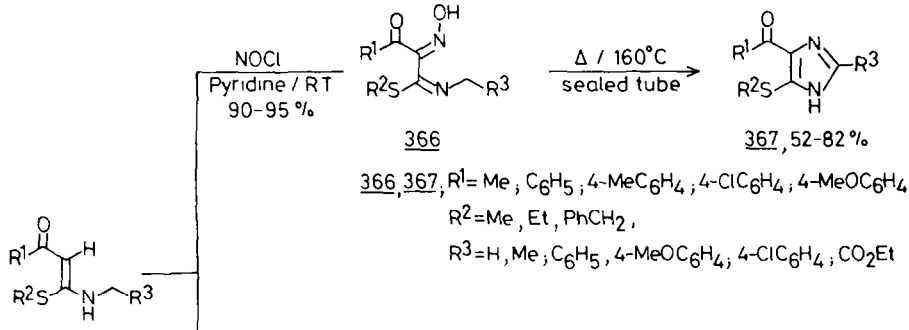
The reaction of S,N-benzylacetals with thionyl chloride to afford 2-aryl 4-acyl 5-methylthiothiazoles[212] was extended by Junjappa and Ila for the synthesis of imidazoles **367** also by reacting the N,S-acetals with nitrosyl chloride in the presence of pyridine to afford hydroxyiminoimines **366**



(105)

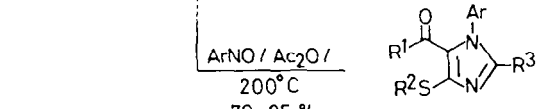
365, $R^1 = C_6H_5$; 4 ClC_6H_4

which underwent thermal cyclodehydration to yield **367** (eq. 106).[213] The N,S-acetals on heating with arylnitroso compounds in the presence of acetic anhydride directly yielded the corresponding 1-arylimidazoles **368** in good yields (eq. 107). Similarly the hydroxyiminoimines **369** derived from



(106)

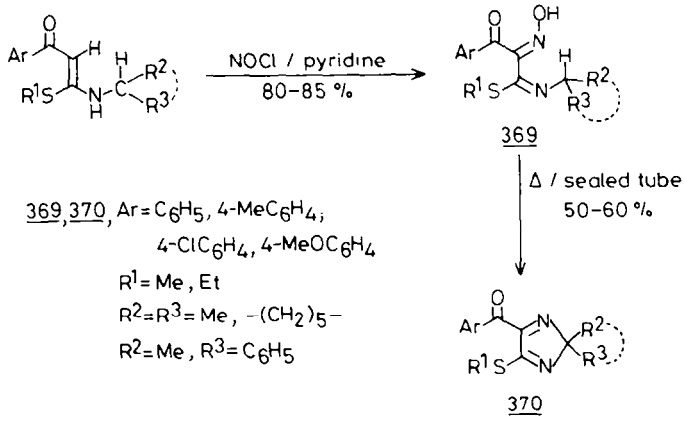
366, 367; R^1 = Me; C_6H_5; 4-MeC_6H_4; 4-ClC_6H_4; 4-$MeOC_6H_4$
R^2 = Me, Et, $PhCH_2$,
R^3 = H, Me; C_6H_5, 4-$MeOC_6H_4$; 4-ClC_6H_4; CO_2Et



(107)

368, R^1 = Me, C_6H_5, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$;
R^2 = Me, Et, C_6H_5; R^3 = H, Me, Et, C_6H_5
Ar = C_6H_5, 4-MeC_6H_4

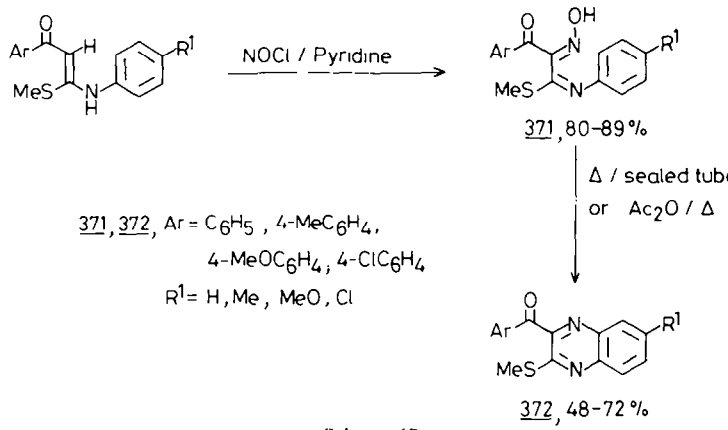
N,S-acetals with isopropyl, cyclohexyl or α-phenylethylamino groups underwent thermal cyclisation to the corresponding 2(H)-imidazoles **370** (eq. 108).[214] When the N-aryl-S-methyl-acetals were



369, 370, Ar = C_6H_5, 4-MeC_6H_4;
4-ClC_6H_4, 4-$MeOC_6H_4$
R^1 = Me, Et
$R^2 = R^3$ = Me, $-(CH_2)_5-$
R^2 = Me, $R^3 = C_6H_5$

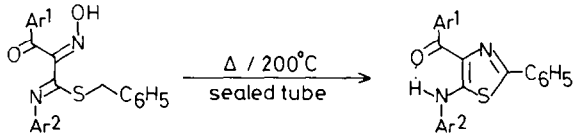
(108)

reacted with NOCl in pyridine, the intermediate hydroxyimino derivative **371** underwent smooth thermal intramolecular ring closure to afford the corresponding quinoxalines **372** (Scheme 67).[213]



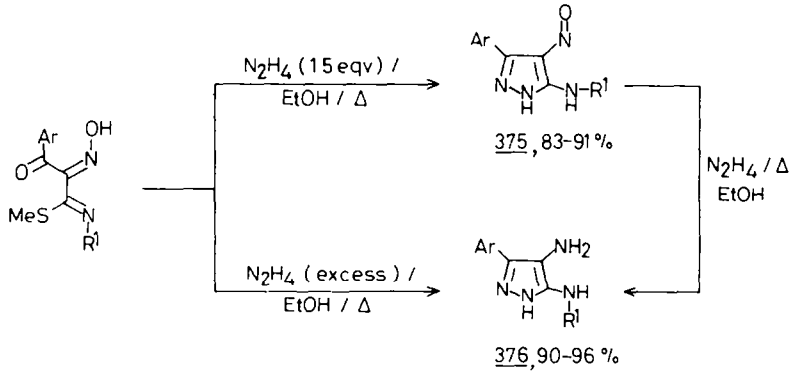
Scheme 67.

Interestingly, when S-methyl group is replaced by benzyl group as shown in hydroxyiminoimine **373**, the course of cyclodehydration was changed involving participation of benzylthio group to afford 2-aryl-5-anilinothiazoles **374** (eq. 109).[213] The hydroxyiminoimines behave like three-carbon

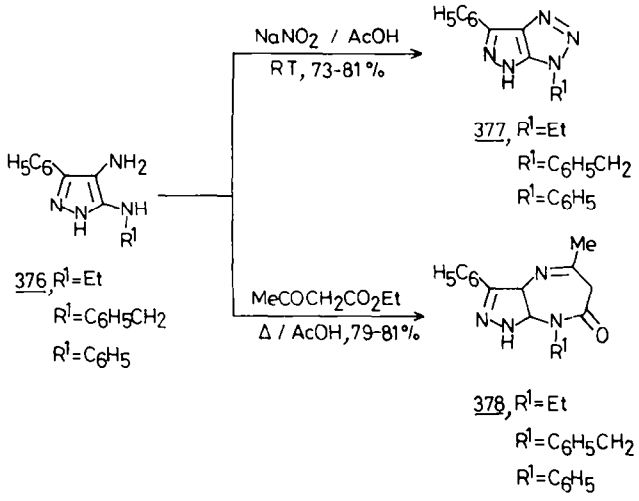


(109)

components when reacted with N_2H_4 to yield the corresponding 4-nitroso-3(5)-alkyl/aryl-aminopyrazoles **375** (Scheme 68) under controlled conditions. However, the 4-nitrosopyrazoles **375** underwent reduction with hydrazine hydrate to afford 4-aminopyrazoles **376** (Scheme 68).[215] The

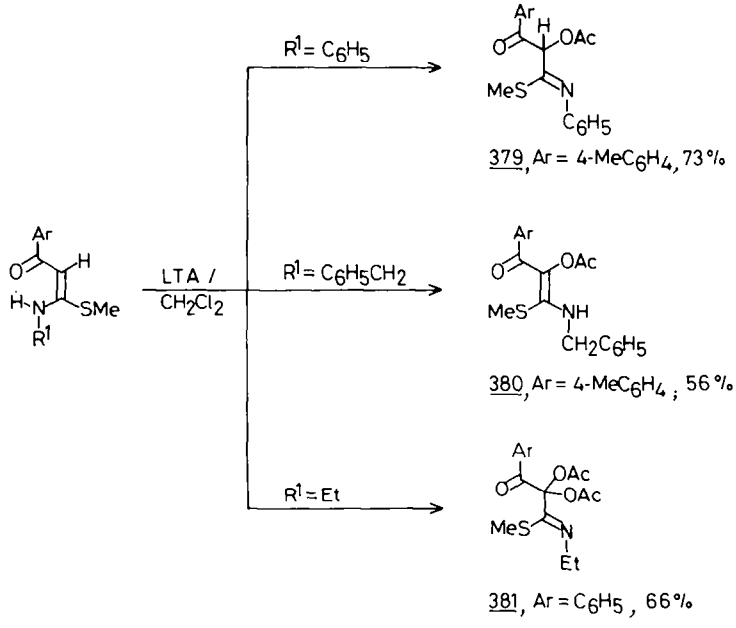


Scheme 68.

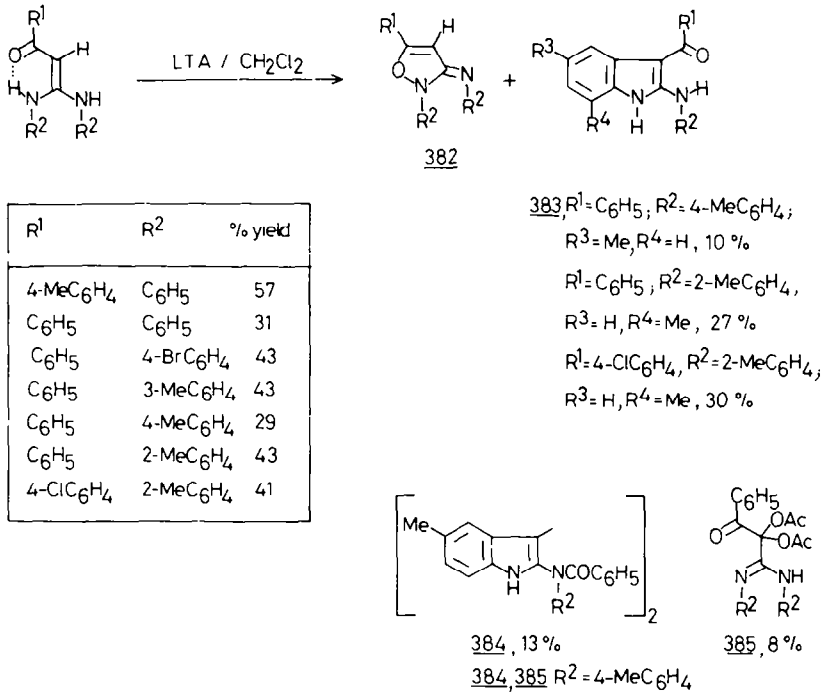


Scheme 69.

4-aminopyrazoles were found to be useful substrates for condensed heterocycles **377** and **378** on diazotization or by treatment with ethyl acetoacetate respectively (Scheme 69). The oxoketene N,S-acetals (R^1 = Ph or $PhCH_2$) underwent oxidation with LTA to afford open-chain α-acetoxy N,S-acetals **379** and **380**, whereas the N-ethyl acetal yielded diacetoxy compound under similar reaction conditions[216] (Scheme 70). However, the N,N-acetals under similar oxidation conditions underwent oxidative cyclisation to afford iminoisoxazolines **382** in moderate yields while the corresponding indoles **383** were also obtained in a few cases (Scheme 71). Only in one case (R^2 = 4-MeC_6H_4), the



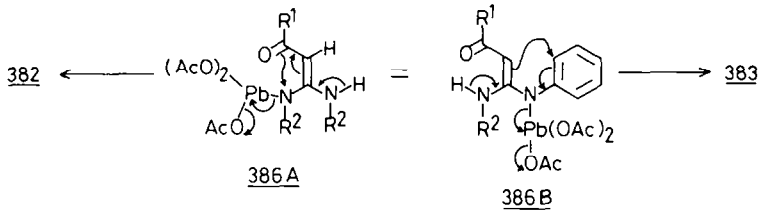
Scheme 70.



R^1	R^2	% yield
4-MeC_6H_4	C_6H_5	57
C_6H_5	C_6H_5	31
C_6H_5	4-BrC_6H_4	43
C_6H_5	3-MeC_6H_4	43
C_6H_5	4-MeC_6H_4	29
C_6H_5	2-MeC_6H_4	43
4-ClC_6H_4	2-MeC_6H_4	41

Scheme 71.

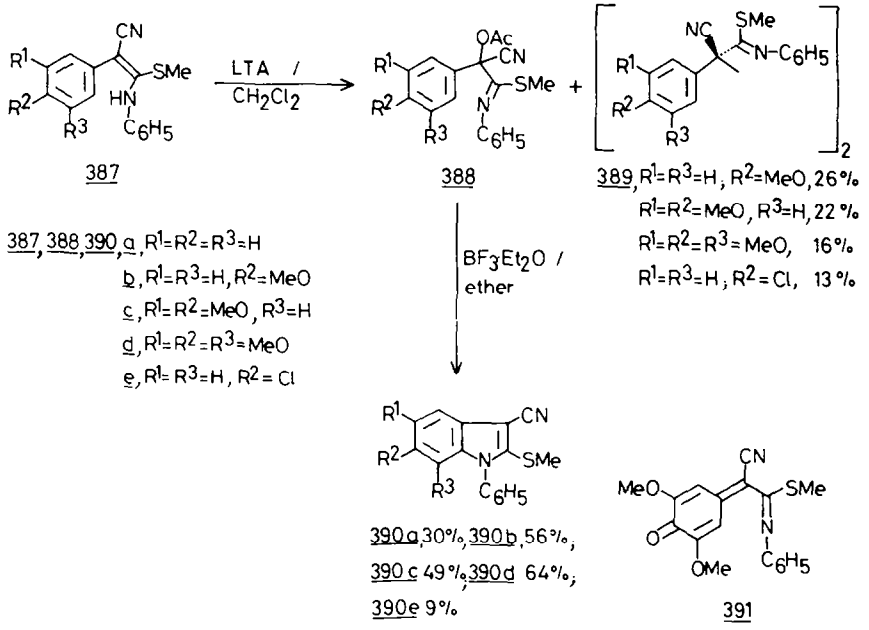
dimeric indole **384** and diacetoxy derivative **385** were isolated in addition to **382** and **383**.[211d] The formation of **382** and **383** is rationalised through the initially formed N-plumbylated adducts **386A** and **386B** respectively (eq. 110). The LTA oxidation of N,S-acetals derived from arylacetonitriles



(110)

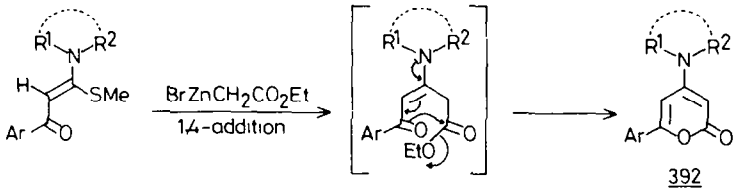
afford iminoacetates **388** and the dimeric products **389** (Scheme 72). The iminoacetates underwent $BF_3 \cdot Et_2O$ assisted cyclisation to the corresponding indole **390** although cyclisation was facile only with those systems carrying methoxy group in the aryl ring, whereas in one case ($R^1 = R^2 = R^3 = OCH_3$) the quinone methide intermediate **391** was also formed in addition to indole (Scheme 72).[217]

The N,S-acetals undergo exclusive 1,4-conjugate addition with organometallic reagents like enaminones. The reaction of Reformatsky reagent ($BrZnCH_2CO_2Et$) with N,S-acetals derived from secondary amines undergo the expected 1,4-addition elimination sequence followed by enol-lactonisation to afford 4-aminopyrones **392** (eq. 111).[218a] The hard electrophilic nature of the β-



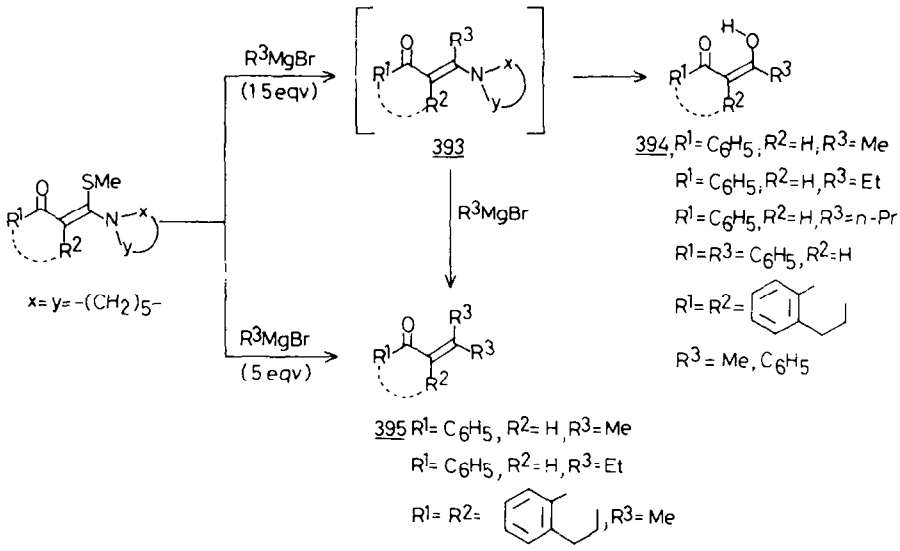
Scheme 72.

carbon in the S,N-acetals is further confirmed by their exclusive 1,4-selectivity towards alkyl and aryl Grignard reagents (Scheme 73). Thus the addition of 1.5 equiv. of alkyl/aryl Grignard reagents to N,S-acetals after work-up yielded the corresponding 1,3-diketones **394** (Scheme 73). When excess Grignard reagents were used, the enaminone intermediate **393** underwent a further 1,4-addition elimination sequence to afford the corresponding β-β-dialkylenones **395** in moderate to good yields (Scheme 73).[218b]



(111)

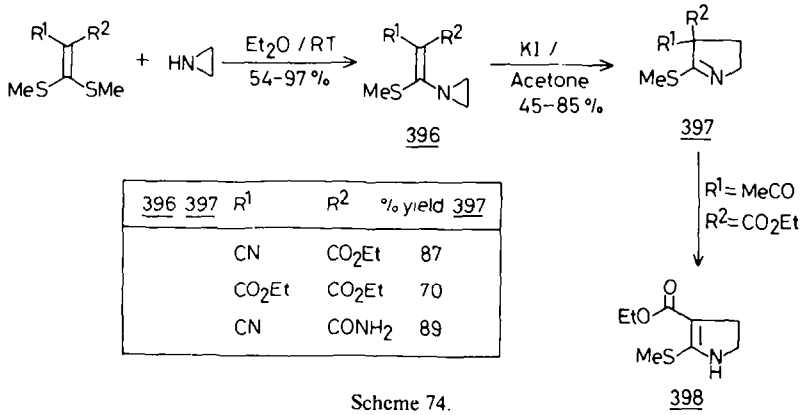
Ar	R^1	R^2	% yield 392
C_6H_5	$-(CH_2)_2-O-(CH_2)_2-$		65
4-ClC_6H_4	$-(CH_2)_2-O-(CH_2)_2-$		68
4-MeC_6H_4	$-(CH_2)_2-O-(CH_2)_2-$		60
4-$MeOC_6H_4$	$-(CH_2)_4-$		72
4-ClC_6H_4	$-(CH_2)_4-$		72
4-MeC_6H_4	$-(CH_2)_4-$		66
4-ClC_6H_4	$-(CH_2)_5-$		69
C_6H_5	Me	Me	62
4-ClC_6H_4	Me	Me	65
4-$MeOC_6H_4$	Me	Me	60



Scheme 73.

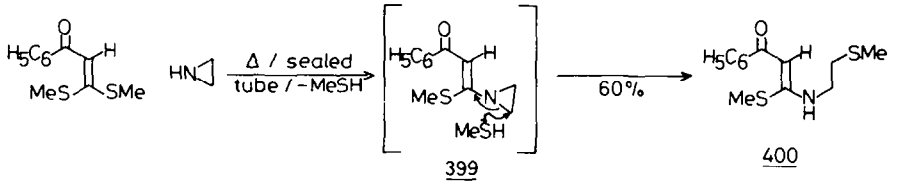
8.3. *Miscellaneous reactions*

Among other amines, the aziridine ring displaces the thiomethyl group only in doubly activated oxoketene dithioacetals to afford 6-aziridinoacetals **396** in high yields without ring rupture.[219] However, when aziridine and oxoketene dithioacetals are heated under drastic conditions (sealed tube), the eliminated methylmercaptan attacks the ring to give the corresponding N,S-acetal **400** (eq. 112). Thus the reaction of aziridine with only doubly activated dithioacetals has been studied. The vinyl aziridines **396** thus prepared undergo facile ring expansion, in the presence of potassium iodide, to afford the corresponding 2-thiomethyl 3,3-disubstituted pyrrolines **397** in high yields[219] (Scheme 74). The cyclic dithioacetals derived from pyrazolines afforded the S,N-aziridinoacetal **401** which on potassium iodide catalysed rearrangement gave the spiro compounds **402** (eq. 113).[219]

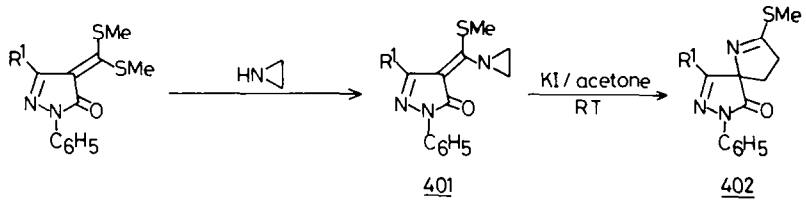


396	397	R^1	R^2	% yield 397
		CN	CO_2Et	87
		CO_2Et	CO_2Et	70
		CN	$CONH_2$	89

Scheme 74.



(112)

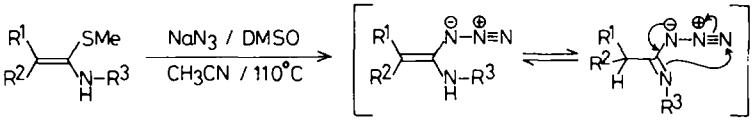


401 402 (113)

401, 402	R^1	% yield 402
	C_6H_5	80
	4-MeC_6H_4	80
	4-$MeOC_6H_4$	74
	4-ClC_6H_4	75
	Me	78

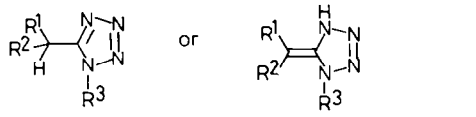
The sodium azide also displaces the methylthio group in oxoketene N,S-acetals to afford the intermediate vinyl azide **403A** which undergoes *in situ* ring closure to give 1,4-disubstituted tetrazoles **404** and/or **405** in good yields (Scheme 75).

However, in the case of N,S-acetals **406** derived from malononitrile, the azide anion undergoes [3+2] cycloaddition with one of the —C≡N groups to afford the corresponding tetrazoles **407** (eq. 114).[189] On the other hand, the tosylazide undergoes [3+2] cycloaddition to mercapto double bond



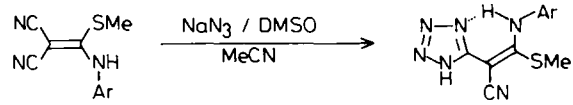
403 A 403 B

R^1	R^2	R^3	% yield 404
4-MeC_6H_4CO	H	C_6H_5	72
4-ClC_6H_4CO	H	C_6H_5	67
C_6H_5CO	H	$C_6H_5CH_2$	63
4-$MeOC_6H_4CO$	H	$C_6H_5CH_2$	64
C_6H_5CO	H	Me	79
C_6H_5CO	H	Et	65
C_6H_5CO	H	n-Pr	74
C_6H_5CO	H	i-Pr	60
C_6H_5CO	H	C_6H_{11}	67
MeCO	H	Et	64
C_6H_5	CN	C_6H_5	76



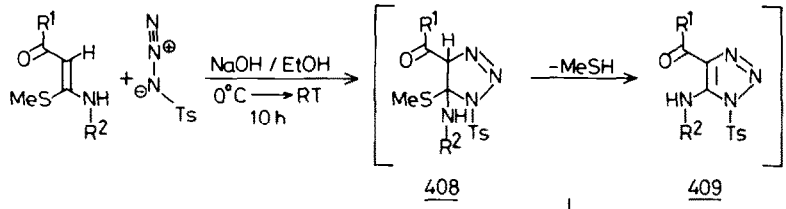
404 or 405, R^1=CO_2Et, R^2=CN, R^3=C_6H_5, 77 %; R^1=CO_2Et, R^2=CN, R^3=$C_6H_5CH_2$, 79 %

Scheme 75.



406 407 (114)

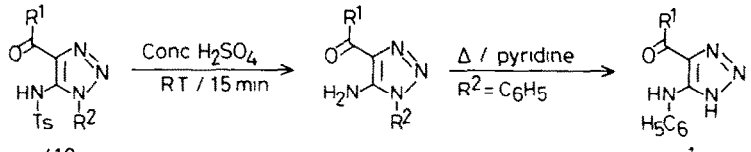
406, 407, Ar = 4-ClC_6H_4



R^1	R^2	% yield 410
C_6H_5	C_6H_5	57
4-ClC_6H_4	C_6H_5	65
C_6H_5	$C_6H_5CH_2$	47
Me	$C_6H_5CH_2$	54
C_6H_5	Me	61
4-MeC_6H_4	Me	54
C_6H_5	Et	68
4-ClC_6H_4	n-Pr	75
C_6H_5	i-Pr	45
4-MeC_6H_4	n-Bu	70
4-ClC_6H_4	c-C_6H_{11}	44
C_6H_5	$CH_2CH(OEt)_2$	56

Scheme 76.

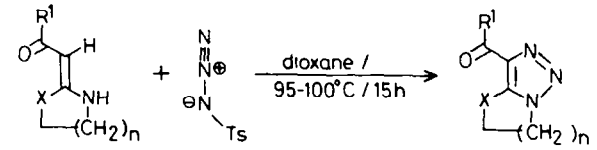
to afford regiospecifically substituted 4-acyl-5-tosylamino-1-aryl/alkyltriazoles **410** obtained via the initially formed triazole **409** through Dimroth rearrangement (Scheme 76).[220] The tosylaminotriazoles **410** were hydrolysed under acidic conditions to afford aminotriazoles **411**, some of them (R^2 = aryl) on heating in pyridine, further underwent Dimroth rearrangement to yield the rearranged triazoles **412** (eq. 115). The corresponding cyclic N,S-acetals and tosylazide also gave



(115)

R^1	R^2	% yield 411
C_6H_5	C_6H_5	95
4-ClC_6H_4	C_6H_5	87
C_6H_5	$C_6H_5CH_2$	89
Me	$C_6H_5CH_2$	84
C_6H_5	Me	75
C_6H_5	Et	82
4-ClC_6H_4	n-Pr	80

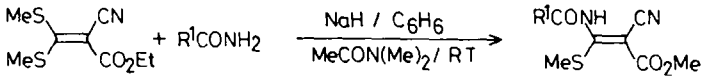
the bicyclic triazoloimidazoles **413** in good yields (eq. 116).[220] Tominaga and co-workers[221] have recently reported the displacement of MeSH group by carboxamides in dithioacetals derived from cyanoacetamide to afford the corresponding N-acylaminoacrylates **414** (eq. 117) which were readily



(116)

413

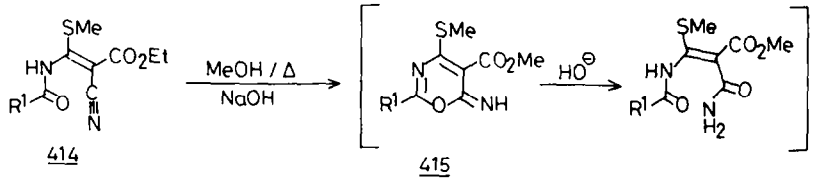
R^1	X	n	%yield 413
C_6H_5	S	1	69
4-ClC_6H_4	S	1	60
4-$MeOC_6H_4$	S	1	65
C_6H_5	NH	1	68
4-ClC_6H_4	NH	1	71
2-thienyl	NH	1	61
C_6H_5	NH	2	69
4-ClC_6H_4	NH	2	73
2-furyl	NH	2	60
2-naphthyl	NH	2	67



(117)

414

R^1	%yield 414
C_6H_5	76
4-$NO_2C_6H_4$	60
4-MeC_6H_4	64
4-$MeOC_6H_4$	39
Me	35
$ClCH_2$	40
$C_6H_5CH{=}CH-$	73

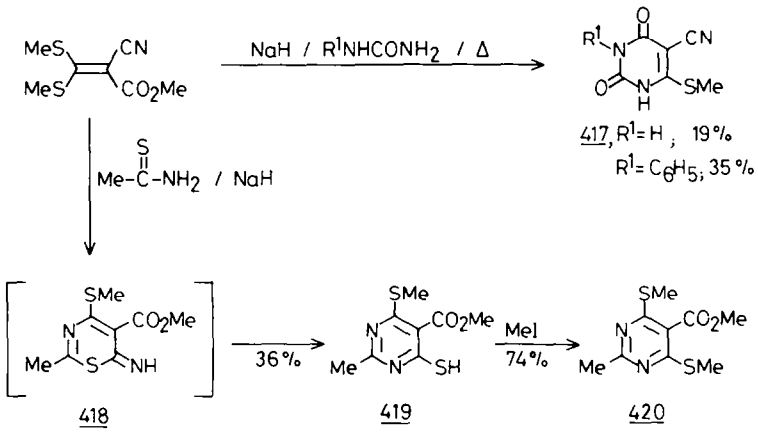


414 415

R^1	%yield 417
C_6H_5	90
4-$NO_2C_6H_4$	96
4-MeC_6H_4	98
4-$MeOC_6H_4$	94
$ClCH_2$	94
$C_6H_5CH{=}CH-$	91

416

Scheme 77.



(118)

(119)

converted to the corresponding pyrimidones **416** through the intermediate **415** (Scheme 77). Similarly, α-cyano- α-carbethoxydithioacetals react with thioacetamide and urea in the presence of NaH to afford pyrimidines **419** and **420** respectively (eq. 118 and 119).[221]

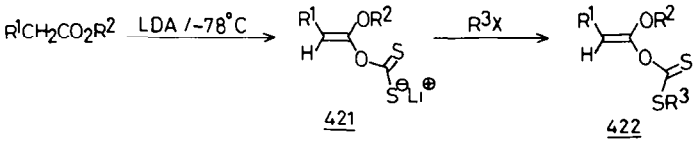
9. CONCLUSION

The α-oxoketene dithioacetals have been shown to be a class of versatile intermediates in many synthetic transformations. They further serve as parent precursors for β-alkylthioenones and enoates, α-oxoketene N,S-, N,N- and O,S-acetals, making them a highly functionalised family of synthons. The two electrophilic centres in α-oxoketene dithioacetals differ in their electrophilicity and thus display hard- soft dissymmetry. The presence of bis(methylthio) groups renders the β-carbon atom into a soft electrophilic centre, while the oxo carbon remains as a hard electrophile thereby permitting a better regioselectivity depending on the hard–soft profiles of nucleophiles. This hard -soft dissymmetry can be reversed under suitable reaction conditions or by replacing one of the alkylthio groups by amino group and the resulting oxoketene N,S-acetals undergo exclusive 1,4-addition with a variety of nucleophiles. This aspect of hard- soft affinity inversion remains to be explored and holds considerable synthetic importance in future.

The success of aromatic annelation through oxoketene dithioacetals has been well established as a new general method. Further exploration of this methodology depends on the generation of suitably functionalised allyl and azaallyl anions. Its extension to heteroaromatic annelation requires further investigation since five- and six-membered heterocycles undergo complete ring deprotonation which at present appears to be a major handicap. The potential application of these intermediates for the construction of a variety of heterocycles has already been emphasised in the earlier review.[1] Many transformations described amply demonstrate that α-oxoketene dithioacetals promise further synthetic potential with the many new reagents appearing in the literature at an increasing rate.

10. ADDENDUM

Tanimoto and co-workers[222] have developed a method for high yield preparation of oxoketene dithioacetals **423** from carboxylic esters (Scheme 78) by reaction of their lithiocnolates with carbon

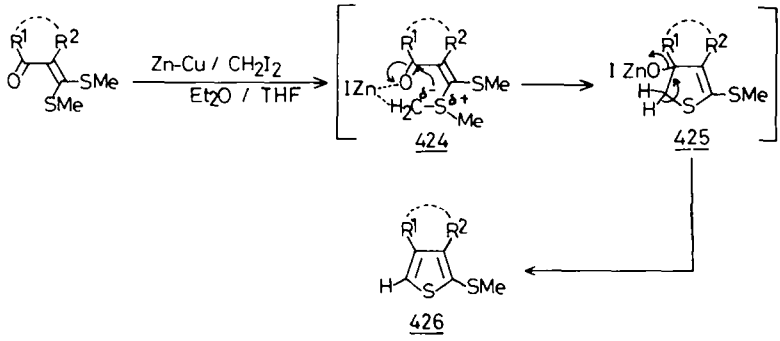


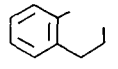
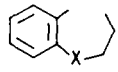
R^1	R^2	R^3	% yield 423
Me	Me	Et	87
Et	Et	Me	82
n-Pr	Me	Et	83
n-Bu	Et	Me	80
n-C_8H_{17}	Et	Me	84
Ph	Me	Et	79

Scheme 78.

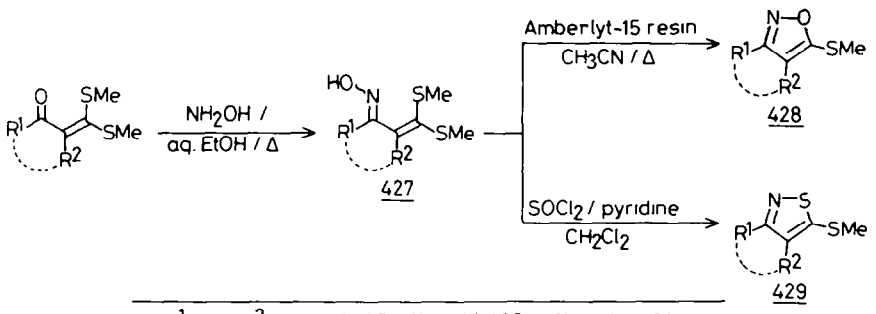
disulphide at −78 °C followed by alkylation. The transformation was shown to proceed through the intermediacy of O-vinyl S-alkyl dithiocarbonates **422**, however, the exact nature of the conversion of **422** to **423** is not clear.

Junjappa, Ila and co-workers have described a new thiophene synthesis by subjecting the α-oxoketene dithioacetals to Simmons–Smith reaction conditions in a one-pot reaction operation.[223] The overall transformation is depicted in Scheme 79. The carbenoid methylene is preferentially attacked by bis(methylthio) sulphur to yield the intermediate ylide **424** which on intramolecular Aldol-type condensation leads to the corresponding 5-methylthio-3,4-substituted and annelated thiophenes in high yields.



R^1	R^2	% yield 426	R^1	R^2	% yield 426
4-MeC_6H_4	H	64	$-(CH_2)_4-$		65
C_6H_5	H	61			62
2-furyl	H	58			
2-thienyl	H	63			
C_6H_5	n-C_3H_7	60			
Me	Me	59			
Me	n-C_4H_9	62	X=O		61
$C_6H_5CH{=}CH-$	H	58	X=S		63

Scheme 79.

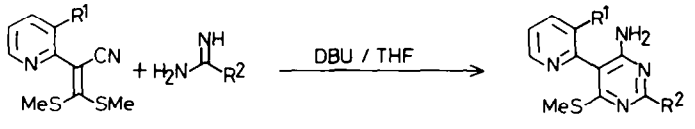


R^1	R^2	% yield 427	% yield 428	% yield 429
$-(CH_2)_4-$		98	40[a], 50[b], 80[c]	84
$-(CH_2)_3-$		99		85, 25[a], 50[b], 73[c]
Et	Me	80	70[a], 88[c]	80
H	H	86	75[c]	60

a with 1·0 mol resin, b with 0·50 mol of resin, c with 0·25 mol resin

Scheme 80.

Dieter and co-workers[224] have recently reported the synthesis of 5-methylthio-isoxazoles **428** and the corresponding isothiazoles **429** in good yields (Scheme 80). The initial oximes **427** obtained from α-oxoketene dithioacetals were cyclised using either Amberlyt-15 resin in refluxing acetonitrile or with thionyl chloride in pyridine to give the respective isoxazole **428** or isothiazole **429** derivatives. Katz and co-workers have extended the earlier pyrimidine synthesis to a new class of substituted 5-(2-pyridinyl)pyrimidines **431** by reacting cyano(2-pyridinyl) ketene dithioacetals **430** with amidines in the presence of DBU as base (eq. 120).[225]



(120)

R^1	R^2	% yield 431
H	Me	69
H	NH_2	56
Br	Me	63
SMe	Me	85

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