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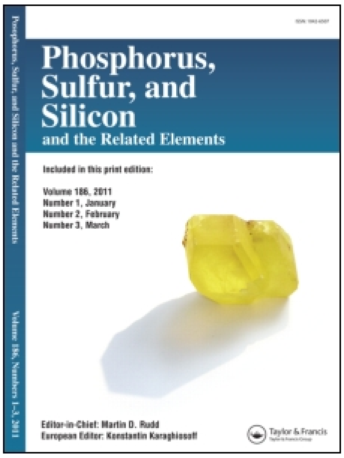

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Thioamide Vinylogs

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REVIEW ARTICLE
Thioamide Vinylogs

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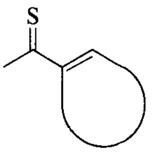
(*Received April 8, 1980*)

Calculations show that the thioamide vinylogs† exhibit a preference for the thioketone(thioaldehyde)-amine structure rather than the thiol-imine tautomeric structure. This is confirmed by spectrometric data, which also make it possible to specify among other things, an ethylenic configuration, the conformation of the molecules and the corresponding rotational barriers. The chemical reactivity of these compounds has been studied; experimentally they undergo electrophilic reactions at the sulphur atom, nucleophilic reactions at the carbon of the thiocarbonyl group and at the carbon attached to the amine and cycloaddition reactions. A wide variety of diversely substituted thioamide vinylogs can be obtained by numerous synthetic methods.

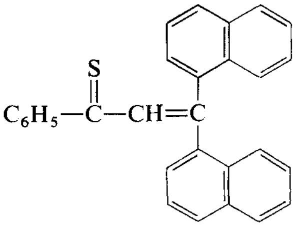
CONTENTS

1 INTRODUCTION

The cyclenic α,β-ethylenic thioketones (**1**) are known to be relatively stable. However, in the acyclic series, the monomeric α,β-ethylenic thioketones obtained at very low temperatures polymerize rapidly on warming.[1] To our knowledge, only 3,3-bis(α-naphthyl)-1-phenyl-2-propene-1-thione (**2**), obtained by the reaction between 5-phenyl-1,2-dithiole-3-one and α-naphthyl magnesium bromide, is described as a stable monomer, steric hindrance probably preventing any polymerisation.[2]



(**1**)



(**2**)

When the lone pair of a heteroatom (S, N ...) is used in the conjugation of the two π bonds of the ethylenic thioketones, the corresponding compounds are relatively stable. This is the case for the dithioester vinylogs. It should be noted, however, that the sulphur attached to carbon 3 is generally endocyclic, and that bicyclic contributions, involving a tetracovalent sulphur atom have been proposed (**3**) to account for the stability.[3]

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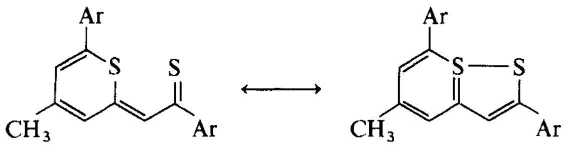
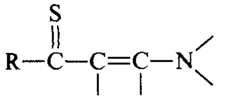
† Only the acyclic thioamide vinylogs have been considered here: those vinylogs for which all or part of the carbon chain 1, 2, 3, is part of a ring are not included.



(3)

The *β*-aminovinylthioketones (**4**) and the *β*-aminovinylthioaldehydes (**4**, R=H) represents another series of interesting compounds.



$$R-\overset{\overset{\displaystyle S}{\|}}{C}-\underset{|}{C}=\underset{|}{C}-N\lt$$

(**4**)

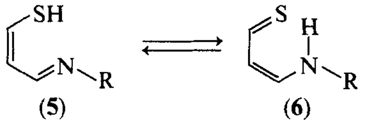
These compounds will be referred to, in this article, as the "thioamide vinylogs," a name which is more indicative of their behaviour. The generic names "enaminothioketones" and "enaminothioaldehydes" should not be used since they imply that the thiocarbonyl is attached to the nitrogen atom and not to carbon 2 of the enamine.

To our knowledge, the first mention of the thioamide vinylogs was in 1964.[4] Since then, some sixty reports or patents have been published giving details of the physicochemical properties, the reactions and the methods of preparation of these compounds.

2 PHYSICOCHEMICAL STUDY: THEORETICAL CALCULATIONS AND SPECTROMETRY

2.1 Thionamine-thiolimine Tautomerism

The differences between the heats of atomization of the thiol (**5**) and thione (**6**) forms were calculated using the SCF-MO-PPP method with Dewar's *σ*, *π* parametrization for the ground states of molecules.[5] In solution, it is advisable to add to these, the differences in solvation energies estimated by using a Born type equation.



(**5**) (**6**)

$\Delta(\Delta H_a)$ (kcal mole^{-1})

R	Gas	$\varepsilon = 2.2$*	$\varepsilon = 48.9$**
H	29.3	33.9	36.0
C_6H_5	28.8	33.1	35.6

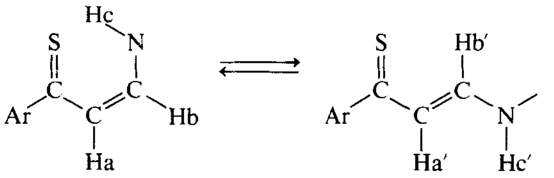
ε : Dielectric permittivity of solvent
* : Corresponds to dioxane, benzene
**: Corresponds to dimethylsulphoxide

The positive values above indicate that the molecules show a preference, energetically, for the thione structure as compared to the thiol tautomeric structure.

In fact, experimentally, spectrometric studies have never detected the thiolimine form.

2.2 Cis-trans Ethylenic Configurations. Rotational Isomers. NMR Spectra

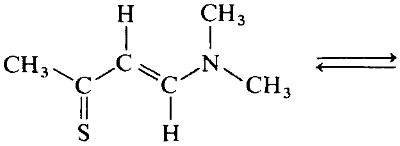
2.2.1 *^{1}H NMR* The thioamide vinylogs containing an NH group (derivatives of ammonia and the primary amines) preferentially adopt a hexagonal geometry: they are thus stabilised by intramolecular hydrogen bonding. However, basic solvents such as hexamethylphosphotriamide (HMPT) tend to break the chelation giving rise to an equilibrium between the chelated form with a cis ethylenic geometry (**7**) and the open form (**8**) with a trans geometry.[6,7]



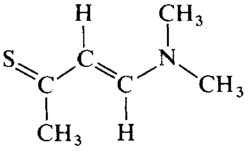
(**7**) (**8**)

	(**7**)	(**8**)
	Jab = 7.6 to 8 Hz	Ja'b' = 11.5 to 12 Hz
	Jbc = 12.6 to 13 Hz	Jb'c' = 12.6 to 13 Hz
$CDCl_3$	100%	0%
HMPT	20 to 25%	75 to 80%

In the case of the vinylogs derived from secondary amines, which have a trans ethylenic configuration, rotational isomers with the so-called "sickle" (**9**) and "W" (**10**) conformations are observed in equilibrium.[8]



(**9**)
S-cis (sickle)
$CDCl_3$, 20°C 64%



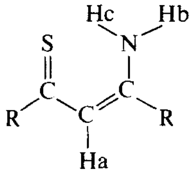
(**10**)
S-trans (W)
36%

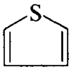
The rotational barrier about the CH—CS bond ($\Delta G^* = 16$ kcal mole^{-1}) is higher than that of the oxygen-containing compounds. When the substituent on the thiocarbonyl is small, the S-trans configuration predominates (95% for H), whereas the S-cis configuration is predominant for large groups (100% for *t*-Butyl).

It is also observed that the two methyl groups, $N(CH_3)_2$, are not equivalent. The activation energy of rotation about the CH—N bond is approximately 15.6 kcal mole^{-1} for the amide vinylogs. This increases to 27.2 for the thioamide vinylogs and is explained by a greater electronic delocalization over the sulphur-containing molecule.

NMR also shows a 7 Hz splitting of the benzyl methylene signal for $C_6H_5C(S)CH{=}CHNHCH_2$-C_6H_5, thus confirming the thionamine structure.[9]

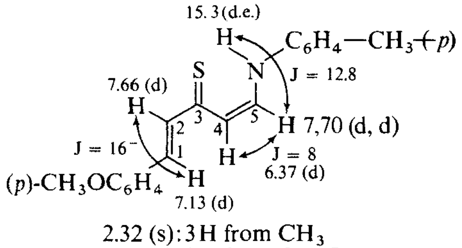
There is also a large difference between the chemical shifts of the two hydrogens attached to the nitrogen; the hydrogen involved in the chelation is shifted strongly downfield.[10]



R	δ Ha	δ Hb	δ Hc
CH_3	6.11	8.93	12.8
C_6H_5	6.95	9.48	13.7
p-$CH_3OC_6H_4$	6.97	9.22	13.3
	7.05	9.20	12.7

A $^4J_{ab}$ coupling of 1.5 Hz is observed for the "W" geometry: on irradiation of Hb, the doublet Ha becomes a singlet.

Finally, we show below a complex spectra, which has been completely interpreted using selectively deuteriated homologs **63**).[11]



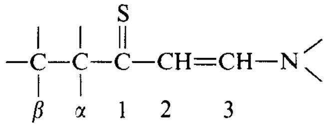
2.32 (s): 3 H from CH_3
3.83 (s): 3 H from CH_3O

$$\left.\begin{array}{l}7.60\ (d)\\ 6.91\ (d)\end{array}\right\}\sum J = 9{:}4H \text{ aromatic} (CH_3OC_6H_4)$$

7.13 (qs): 4 H aromatic ($CH_3C_6H_4$)
Solvent: $CDCl_3$

2.2.2 ^{13}C *NMR*

The ranges for the chemical shifts for the thioamide vinylogs as compared to the corresponding amide vinylogs[12] are given below. The numbers given in brackets correspond to the difference: ($\delta_{TV} - \delta_{AV}$).



$$-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{S}{\overset{\|}{C}}-CH{=}CH-N\langle$$

β α 1 2 3

C_α:	32-48 ppm	(8-11)
C_1:	206-236	(17.6-33.9)
C_2:	109-119	(16.1-18.1)
C_3:	146-164	(0.4-5.7)

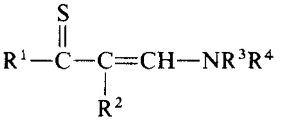
The chemical shifts of C_1 increase with the substitution of C_α.

The chemical shifts of C_2 decrease with the substitution of C_α: this can be attributed to the interaction between the hydrogens attached to C_2 and C_β in the S-cis conformation.

The resonance signals of the carbon atoms (C_1, C_2, C_α) are shifted noticeably downfield compared to the corresponding oxygen-containing compounds. Due to the high polarisability of the thiocarbonyl group, the sulphur is negative and, correspondingly, the neighbouring carbon atoms are positive.

2.3 *UV-Visible Spectra*[13,14]

The principal maximum due to the π → π* transition is considerably shifted towards the higher wavelengths as compared to the oxygen-containing parent compounds.



$$R^1-\overset{S}{\overset{\|}{C}}-\underset{R^2}{\underset{|}{C}}{=}CH-NR^3R^4$$

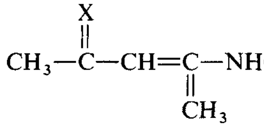
R^1	R^2	R^3	R^4
CH_3	H	CH_3	CH_3
iC_3H_7	H	C_2H_5	C_2H_5
C_6H_5	C_6H_5	CH_3	CH_3
C_6H_5	C_6H_5	C_2H_5	C_2H_5
C_6H_5	C_6H_5	$CH_2C_6H_5$	$CH_2C_6H_5$
C_6H_5	C_6H_5	$(CH_2)_4$	
C_6H_5	C_6H_5	$(CH_2)_5$	
C_6H_5	C_6H_5	$(CH_2)_2$—O—$(CH_2)_2$	

$\lambda_{max}^{CH_3OH}$(log ε)		
383(4.38)	247(3.67)	218(3.94)
397(4.35)	251(3.83)	217(3.97)
500(2.90)	430(4.12)	390(4.23)
510(2.83)	430(4.11)	390(4.31)
520(2.46)	435(4.91)	390(4.36)
525(2.81)	430(4.09)	395(4.36)
520(2.94)	435(4.21)	395(4.30)
530(2.77)	430(4.15)	395(4.26)

2.4 *IR Spectra*

The position of the free ν_{NH} is known for the amide vinylogs, but not for the thioamide vinylogs. The authors[7] consider that the same value: 3460 cm^{-1} may be adopted and the strength of the intramolecular chelation expressed as $\Delta\nu = 3460 - \nu_{NH}$ chelated.

Therefore, for:



$CH_3{-}\overset{\overset{\displaystyle X}{\|}}{C}{-}CH{=}\underset{\underset{\displaystyle CH_3}{\|}}{C}{-}NHC_3H_7$ $X = S, O$

$\Delta\nu = 3460\text{-}2740 = 720$ for $X = S$

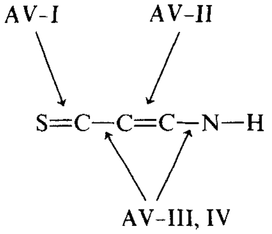
$= 3460\text{-}3180 = 280$ for $X = O$

The intramolecular chelation is much stronger in the N—H···S=C association than in the N—H···O=C association.

On the other hand, it is the Authors' opinion that intermolecular associations are stronger for CO than for CS: the broad band of the pyrrolethione hydrogen bond at 3290 cm^{-1} disappears upon dilution more readily than the pyrrolecarbonyl bond.

The deformation vibration δ_{NH} is shown to be at 1585-1587 cm^{-1}, as this disappears on deuteriation.[15] A broad band γ_{NH} in the region 786-802 cm^{-1} is attributed to out-of-plane deformation.

In these compounds, the vibrations seem to be strongly coupled and therefore interpretation of the spectra is difficult. The Authors[49] have distinguished 4 main bands or zones between 1800 and 400 cm^{-1}:



Although, in the literature, a C=S (aliphatic) band is found between 1170 and 1220 cm^{-1} and a C=S (aromatic) band between 1240 and 1270 cm^{-1}, here the case is different as there is no isolated C=S vibration.

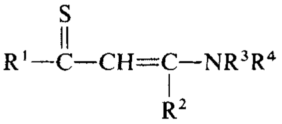
AV-I has only a C=S character. In the compounds with a cis ethylenic geometry, the vibration appears between 1105 and 1116 cm^{-1}. In the compounds with a trans geometry (in solution in dimethylsulphoxide) shoulders appear at 1130-1135 cm^{-1}.

AV-II, with a C=C character, lies between 1602 and 1631 cm^{-1}.

AV-III, between 1492 and 1498 cm^{-1}, and AV-IV, between 1266 and 1296 cm^{-1}, are coupled valence vibrations dominated by the C—C and C—N character.

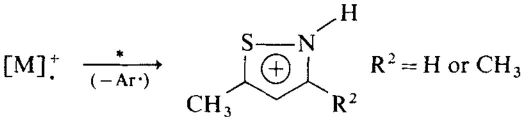
2.5 *Mass Spectra*

The molecular peak is always present, often very strong.[16]

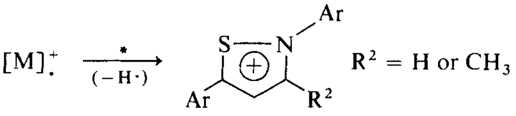


$R^1{-}\overset{\overset{\displaystyle S}{\|}}{C}{-}CH{=}\underset{\underset{\displaystyle R^2}{|}}{C}{-}NR^3R^4$

With $R^1 = CH_3$, $R^2 = H$ or CH_3, $R^3 = H$, $R^4 = C_6H_5$, the ion $[M{-}C_6H_5]^+$ is the base peak,



With R^1 and R^4 = Aryl, $R^2 = H$ or CH_3, $R^3 = H$, the molecular peak is even stronger, the base peak is $[M{-}H]^+$.



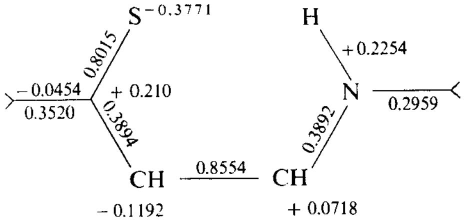
With an aliphatic secondary amine substituent (e.g. $NR^3R^4{=}NHCH_3$), the molecular ion is the base peak.

With an aliphatic tertiary amine substituent (e.g. $NR^3R^4{=}N(CH_3)_2$ or $N(C_2H_5)_2$), the most abundant peak is $[M - 33]^+$ due to the loss of SH·.

The loss of SH· appears to be general and is observed on all the spectra. The origin of the hydrogen remains to be specified.

2.6 Molecular Diagrams and Reactivity

An example of the molecular diagram is given below (**11**)[17]



11

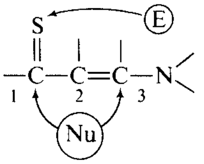
(C_6H_5—CS—CH=CH—NHC_6H_5)

with the net charges and the π bond orders.

The polarisation energies (according to Wheland) have been calculated for the electrophilic (E) and nucleophilic (Nu) reactions. Electrophilic attacks proceed in the order of N, S, C_2, C_3, C_1 and therefore the inverse order is true for the nucleophilic attacks.[7]

According to calculation, the nitrogen is the first centre of electrophilic attack. At low temperatures this has been verified for the enamines. Experimentally, this result was not found for the thioamide vinylogs, however the low solubility of these compounds hinders experiments carried out below room temperature.

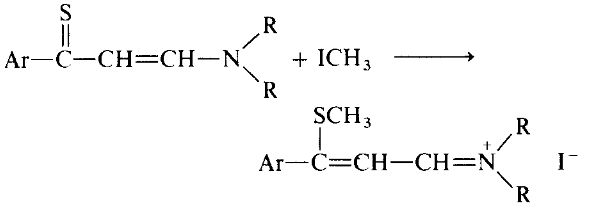
Experimental reactivity:



3 REACTIONS OF THE THIOAMIDE VINYLOGS

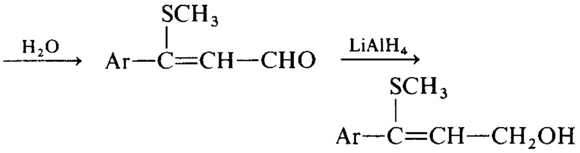
3.1 Electrophilic and Nucleophilic Reactions

3.1.1 Electrophilic reactions at the sulphur Alkylation occurs at the sulphur atom: the iminium group can be hydrolysed to the aldehyde (**12**) for N-alkyl derivatives and deprotonated to the imine (**13**) for primary arylamine derivatives.[18,19]



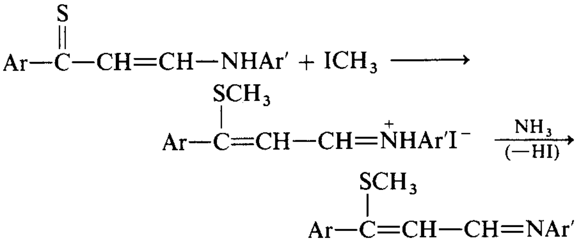
$$\mathrm{Ar{-}C({=}S){-}CH{=}CH{-}NR_2 + ICH_3 \longrightarrow Ar{-}C(SCH_3){=}CH{-}CH{=}\overset{+}{N}R_2\ I^-}$$

NRR=pyrrolidine, piperidino, morpholino



$$\xrightarrow{\mathrm{H_2O}} \mathrm{Ar{-}C(SCH_3){=}CH{-}CHO} \xrightarrow{\mathrm{LiAlH_4}} \mathrm{Ar{-}C(SCH_3){=}CH{-}CH_2OH}$$

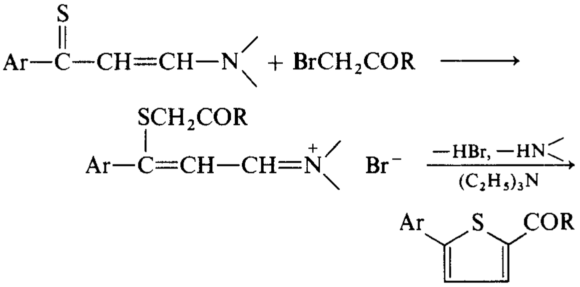
(**12**)



$$\mathrm{Ar{-}C({=}S){-}CH{=}CH{-}NHAr' + ICH_3 \longrightarrow Ar{-}C(SCH_3){=}CH{-}CH{=}\overset{+}{N}HAr'I^-} \xrightarrow[\mathrm{(-HI)}]{\mathrm{NH_3}} \mathrm{Ar{-}C(SCH_3){=}CH{-}CH{=}NAr'}$$

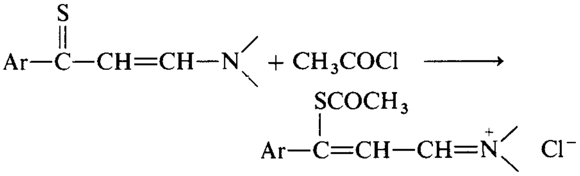
(**13**)

With α-bromomethylketones, the iminium salt undergoes further reaction to give the 2-acyl thiophenes (**14**).[20–24]



(**14**)

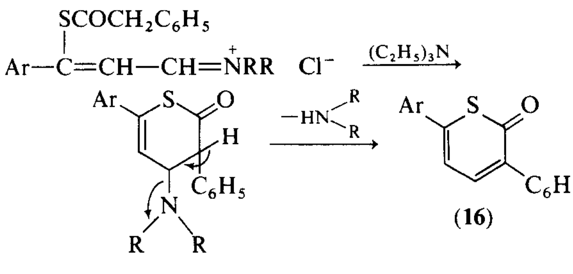
Acylation also takes place at the sulphur but the resulting iminium chloride is unstable (**15**).



$$\mathrm{Ar{-}C({=}S){-}CH{=}CH{-}N\!< + CH_3COCl \longrightarrow Ar{-}C(SCOCH_3){=}CH{-}CH{=}\overset{+}{N}\!<\ Cl^-}$$

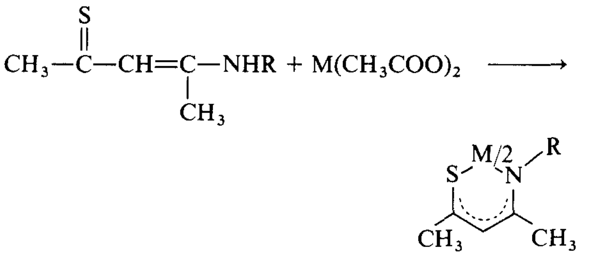
(**15**)

An analogous reaction is obtained with the chloride of phenylacetic acid. By adding triethylamine, the iminium chloride undergoes further reaction to give a thiopyranone (**16**).[20]

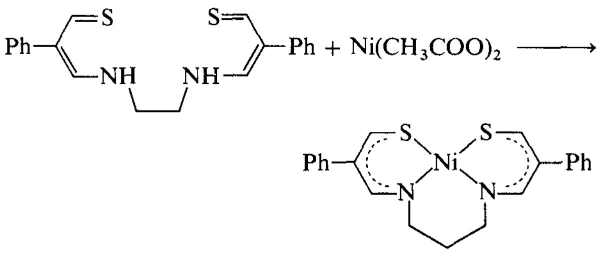


(**16**)

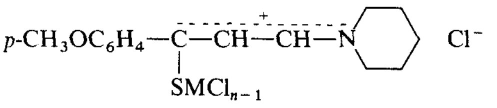
The salts of Co, Ni, Zn ... (generally acetates) give complexes with the thioamide vinylogs.[9,25–27] The planar and tetrahedral structures of the chelated metal ligands are in rapid equilibrium. The planar complex formed with the thioamide vinylogs is observed to be much more stable than the chelations formed with the amide vinylogs.



(**17**)



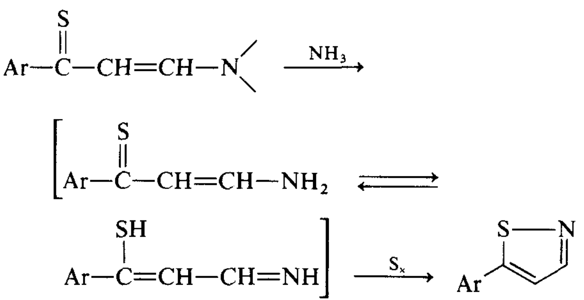
By simply mixing their solutions in ethanol, the thioamide vinylogs, derived from secondary amines, and mercury, antimony and bismuth chlorides give yellow or yellowish-orange precipitates (**18**) for which the composition appears to correspond to 1:1 complexes.[19]



(**18**)

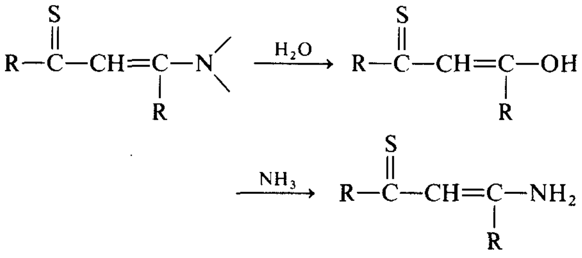
3.1.2 *Nucleophilic reactions at carbons 1 and 3*

Ammonia In the presence of elemental sulphur, ammonia gives isothiazoles (**19**).[19]*

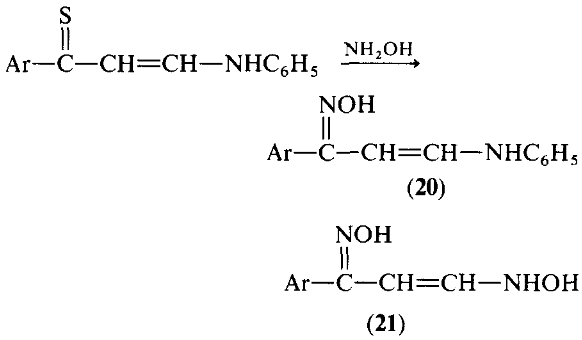


(**19**)

The intermediate vinylog, with no substituent at the nitrogen, was isolated only when carbons 1 and 3 were identically substituted. The reaction occurs only in the presence of aqueous ammonia. Intermediary hydrolysis to β-thioxoketone has been postulated.[10,28]



Hydroxylamine Oximation can occur selectively on the thiocarbonyl group (**20**) when the vinylog is derived from an arylamine; an excess of hydroxylamine leads to transamination (**21**).[4,29,30]

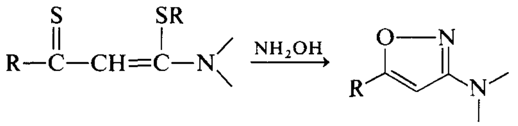


(**20**)

(**21**)

The resulting compound (**21**), which can be considered as the dioxime of 3-aryl-3-oxo-propanal, is obtained only in the N-alkyl series.

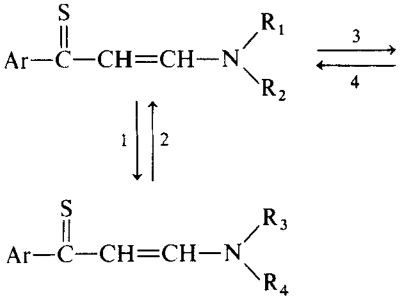
When the vinylog contains an SR group, the substitution of this group by hydroxylamine leads to the cyclisation to an isoxazole (**22**).[25]



(**22**)

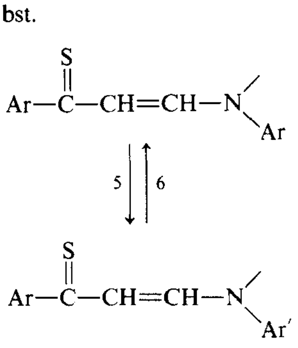
Amines The transamination of the thioamide vinylogs is a very general reaction (Reactions 1 to 6).[31] The alkylamine and arylamine groups on the vinylogs can be substituted for other alkylamines and arylamines, using as reactant the amine acetate (possibly the chlorohydrate) in ethanol.

The transaminations 3, 5 and 6 by free arylamine groups are also carried out in ethanol, in these conditions the alkylamines do not appear to interchange (Reactions 1 and 2) and only transaminate the crowded arylaminopropenethiones (Reaction 4).[30]



$$\mathrm{Ar{-}\overset{S}{\overset{\|}{C}}{-}CH{=}CH{-}N\begin{smallmatrix}R_1\\R_2\end{smallmatrix}} \;\underset{4}{\overset{3}{\rightleftarrows}} \qquad \overset{1}{\downarrow}\;\overset{2}{\uparrow} \qquad \mathrm{Ar{-}\overset{S}{\overset{\|}{C}}{-}CH{=}CH{-}N\begin{smallmatrix}R_3\\R_4\end{smallmatrix}}$$

R_1, R_2, R_3 and R_4: aliph. subst.

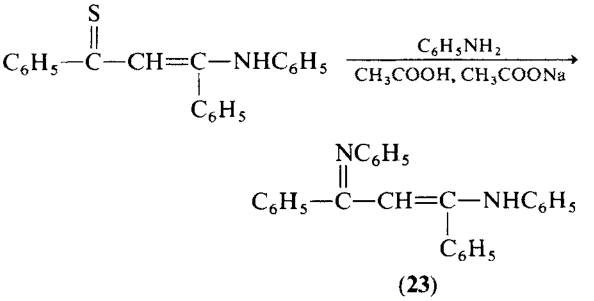


$$\mathrm{Ar{-}\overset{S}{\overset{\|}{C}}{-}CH{=}CH{-}N\begin{smallmatrix}\diagup\\Ar\end{smallmatrix}} \qquad \overset{5}{\downarrow}\;\overset{6}{\uparrow} \qquad \mathrm{Ar{-}\overset{S}{\overset{\|}{C}}{-}CH{=}CH{-}N\begin{smallmatrix}\diagup\\Ar'\end{smallmatrix}}$$

Ar, Ar′: arom. subst.

In the reactions above, it is conceivable that the amine also reacts weakly on the thiocarbonyl group. This reaction can be shown more easily when the amine-reagent is the one entering the vinylog. However, practical conditions are sometimes different from those in the transaminations above.

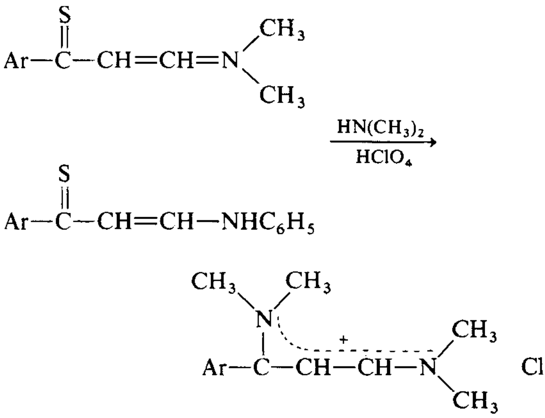
Thus aniline, in solution in acetic acid and in the presence of sodium acetate reacts with 3-anilino-1,3-diphenyl-2-propene-1-thione to give an iminopropenamine (**23**) with a 20% yield.[32]



$$\mathrm{C_6H_5{-}\overset{S}{\overset{\|}{C}}{-}CH{=}\underset{C_6H_5}{\underset{|}{C}}{-}NHC_6H_5} \xrightarrow[\mathrm{CH_3COOH,\,CH_3COONa}]{\mathrm{C_6H_5NH_2}} \mathrm{C_6H_5{-}\overset{NC_6H_5}{\overset{\|}{C}}{-}CH{=}\underset{C_6H_5}{\underset{|}{C}}{-}NHC_6H_5}$$

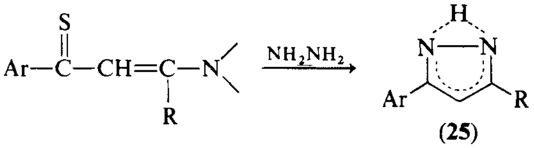
(**23**)

A secondary amine enables the isolation of a vinamidium salt (24) (transamination may occur when the amine reagent is different from the amine group on the vinylog substrate).[33]



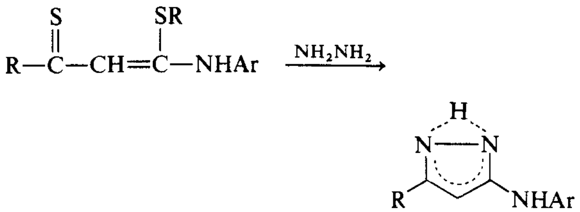
(**24**)

Hydrazine Reaction with hydrazine gives pyrazoles (**25**).[19]



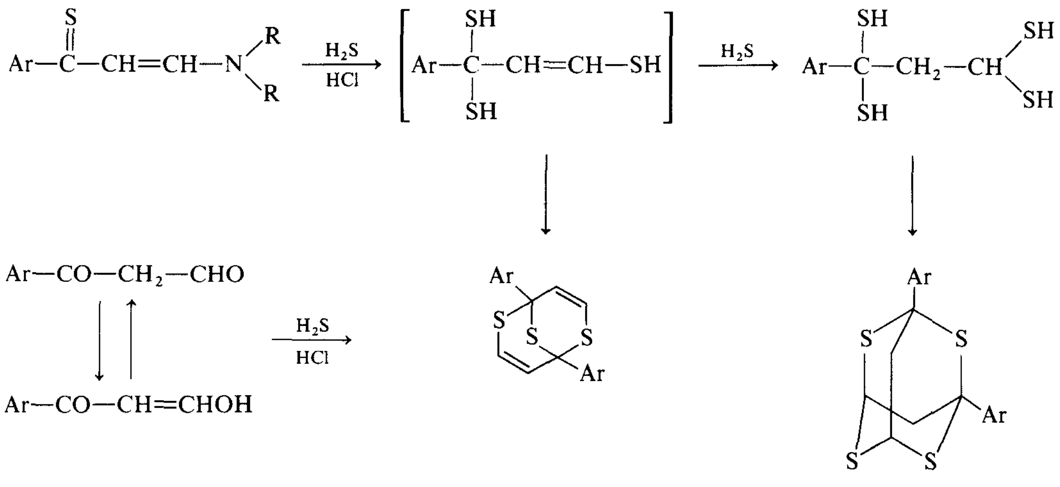
(**25**)

When the vinylog contains an SR group in position 3, this group is eliminated on cyclisation (**26**).[26]



(**26**)

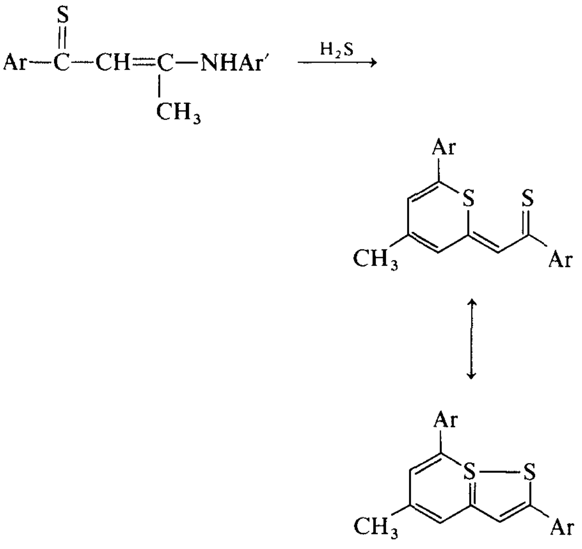
Hydrogen sulphide The molecule is progressively saturated with mercapto groups. Following elimination of the amine, bimolecular cyclisations (**27**) and (**28**) occur.[34] The compounds (**27**) are also obtained starting from the corresponding β-ketoaldehydes.



(27) (28)

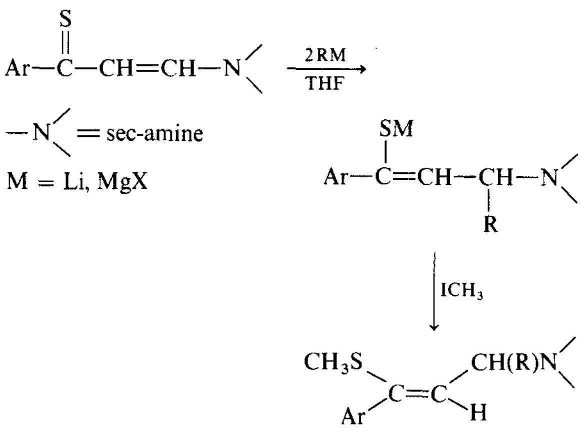
These reactions interfere in the preparation of the thioamide vinylogs from the amide vinylogs and restrict yields.

The vinylogs containing a methyl substituent in 3, give the α-(2-thiopyranylidene)-thioacetophenones (**29**).[35]



(29)

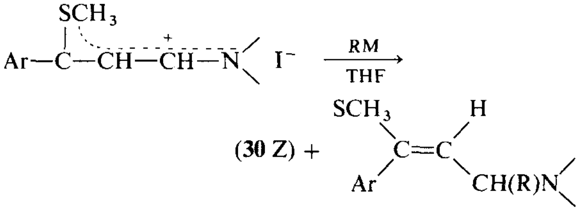
Organomagnesium and organolithium compounds Nucleophilic attack of carbon 3 of the vinylog by organomagnesium (or lithium) compounds at 0°C (or at −80°C), results in a 1,4-addition reaction.[36,37]



(30 Z)

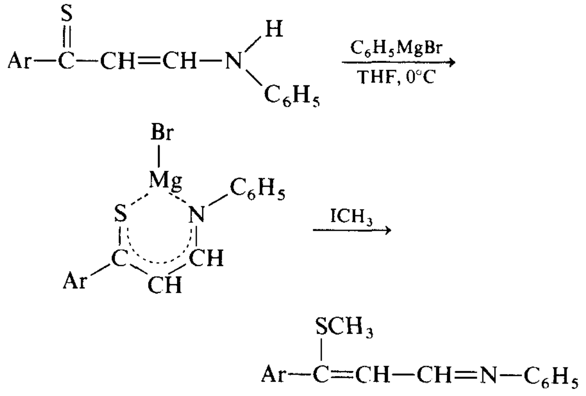
On alkylation, the α,β-unsaturated thioether (**30**), with a Z configuration, is obtained. The stereospecificity of this reaction is probably due to an initial complexation of the thioamide vinylog by a first mole of organometallic (linking the metal both to the sulphur and the nitrogen).

The reaction of the organometallics on the iodomethylated thioamide vinylogs (3.1.1) gives, on the contrary, a mixture of Z and E isomers.



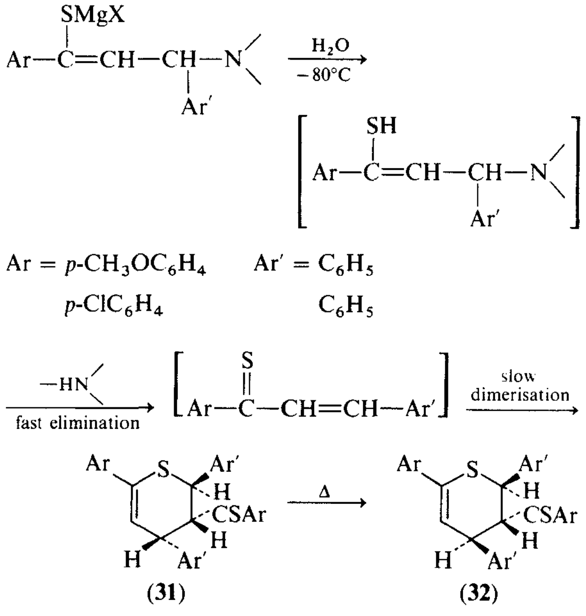
(30 E)

When the thioamide vinylog is a derivative of a primary amine, hydrogen-metal exchange takes place.



(13)

Neither the aminated and possibly enethiolized thioketone, nor its elimination product, the ethylenic thioketone, are isolated after hydrolysis of the product of the addition of an arylmagnesium halide to a thioamide vinylog. The only compound obtained is, in fact, the dimer of the ethylenic thioketone 31).

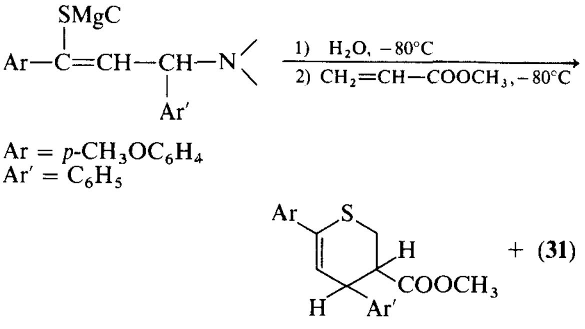


Ar = p-$CH_3OC_6H_4$ Ar′ = C_6H_5
p-ClC_6H_4 C_6H_5

(31) (32)

The 3,4-dihydro-2H-thiopyran (31) undergoes thermal isomerisation to its epimer (32), in which the bulk substituents (aromatic and thiocarbonyl groups) are arranged alternatively on both sides of the dihydrothiopyran ring.[38]

The thiochalcone has been shown to exist, *in situ*, by reacting it with another dienophile.

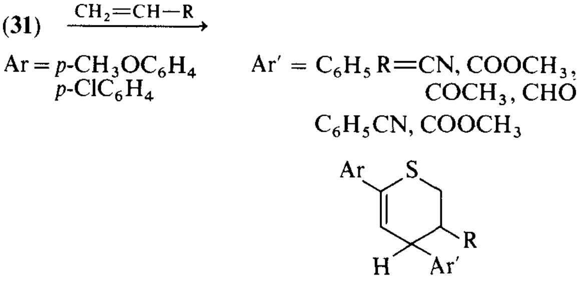


Ar = p-$CH_3OC_6H_4$
Ar′ = C_6H_5

(33)

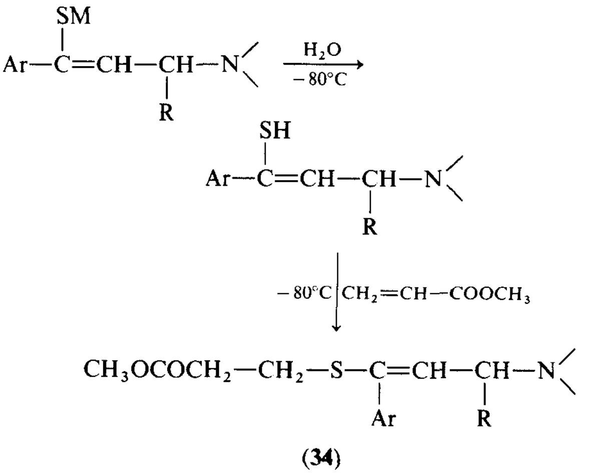
(33) is obtained with a yield of 9%, (31) with a yield of 55%.

Compounds of type (33) may also be obtained with excellent yields by heating the dimer (31) with an acrylic compound under reflux.



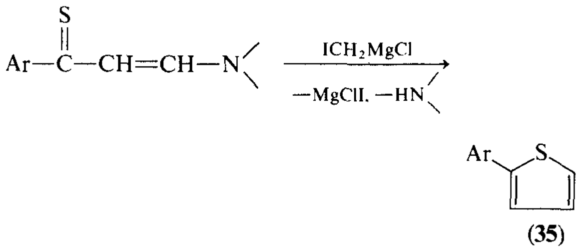
Ar = p-$CH_3OC_6H_4$ Ar′ = C_6H_5 R=CN, $COOCH_3$,
p-ClC_6H_4 $COCH_3$, CHO
C_6H_5CN, $COOCH_3$

When the thioamide vinylog is substituted in the 3 position by an aliphatic group, the presence of the thioketone-amine in the reaction medium has been verified by the addition of methyl acrylate at −80°C after hydrolysis (34).



(34)

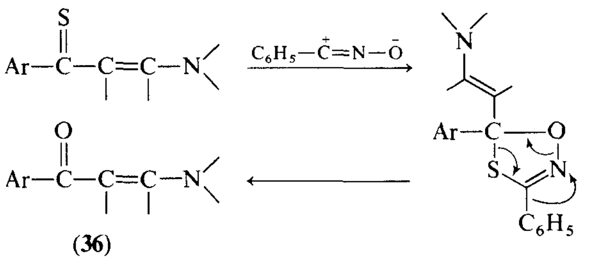
After elimination of the amine, iodomethylmagnesium chloride gives the thiophene derivative **(35)**.



(35)

3.2 *Cycloaddition Reactions*

Benzonitrile oxide undergoes a dipolar addition on the thiocarbonyl group. The oxathiazole intermediate has not been isolated: it decomposes to give the amide vinylog. To our knowledge, this is the only reaction which has been described enabling the conversion of the thioamide vinylogs into their oxygen-containing homologs **(36)**.[32,39]

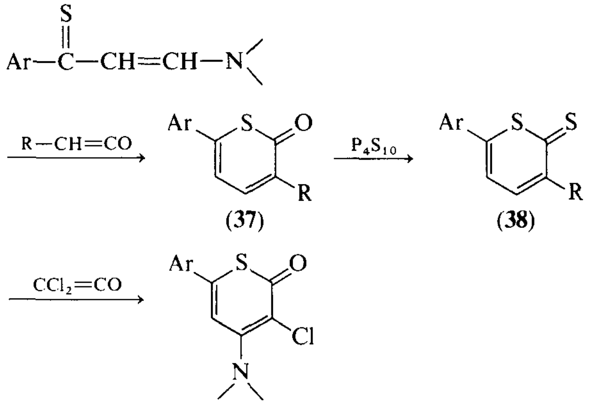


(36)

We have already mentioned in 3.1.1 and 3.1.2 the reactions which can be considered as (4 + 1) cycloadditions giving thiophene and isothiazole rings and (4 + 2) cycloadditions giving thiopyranones.

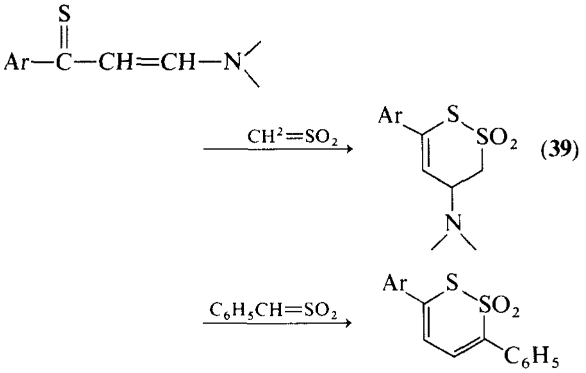
The thioamide vinylogs behave as heterodienes undergoing (4 + 2) Diels–Alder reactions with various dienophiles: ketenes, sulphenes; aldehydes, ketones, esters, nitriles and acrylic amides; carbocyclic and heterocyclic compounds possessing an endocyclic double bond.

Ketenes The ketenes and the acid chlorides (potential ketenes), when reacted with the thioamide vinylogs, give 2-(2H)-thiopyranones **(37)** which can be converted into 2-(2H)-thiopyranthiones **(38)**.[20–22]



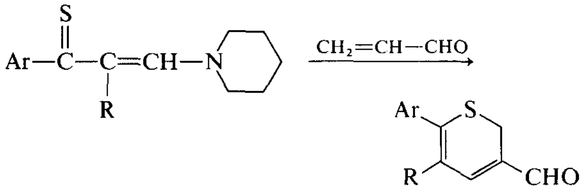
(37) **(38)**

Sulphenes The sulphenes give either simple addition compounds: 5-amino-5,6-dihydro-1,2-dithiine-1,1-dioxides **(39)** or addition-elimination compounds: 1,2-dithiine-1,1-dioxide **(40)**.[24,40]



(39) **(40)**

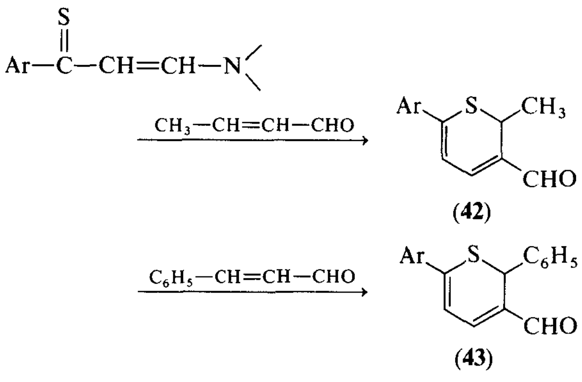
Acrylic aldehydes With acrolein, the 3-carbaldehyde-(2H)-thiopyrans are obtained **(41)**.[41,42]



(41)

Ar = C_6H_5, p-$CH_3OC_6H_4$
R = H, Cl

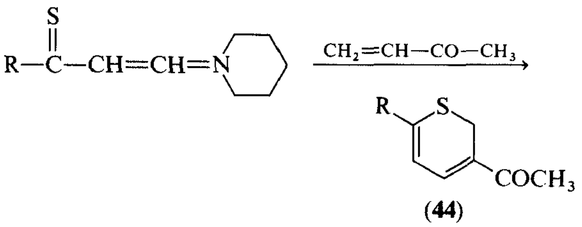
Crotonic and cinnamic aldehydes behave similarly giving compounds **(42)** and **(43)** respectively.[41]



(42)

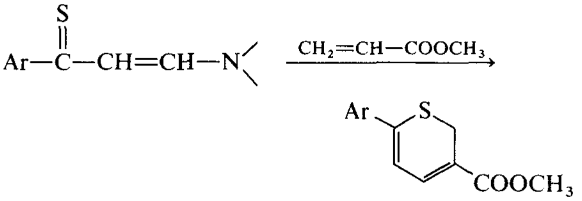
(43)

Acrylic ketones Methylvinylketone gives the 1-(3-(2 H)-thiopyranyl) ethanones (**44**).[41,42]



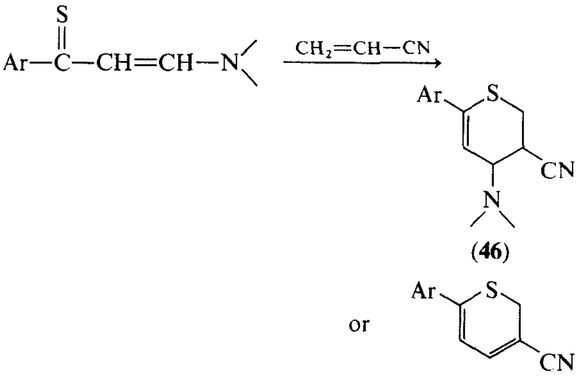
(**44**)

Acrylic esters With methyl acrylate, 3-methylcarboxylate-(2 H)-thiopyrans are obtained (**45**).[43]



(**45**)

Acrylic nitriles With acrylonitrile, addition and addition-elimination compounds, (**46**) and (**47**), are obtained.[41–43]



(**46**)

or

(**47**)

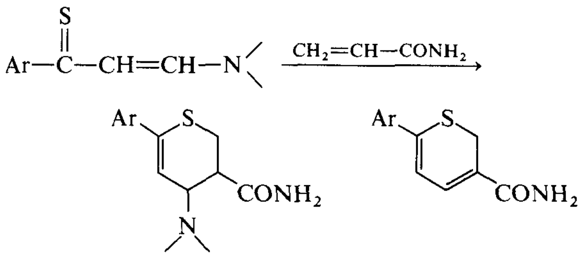
The kinetics of the addition of the thioamide vinylog

(—N⟨ = piperidine)

on the acrylonitrile have been studied (order 2:1 with respect to each reactant).

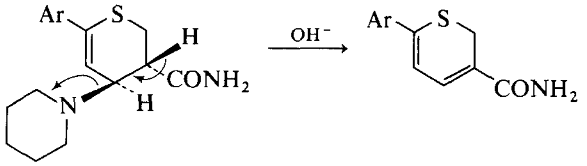
	k (l · mole^{-1} sec.$^{-1}$)
Ar = p-$CH_3OC_6H_4$	1.2
p-BrC_6H_4	1.7
p-$CH_3C_6H_4$	2.0

Acrylic amides Addition (**48**) and addition-elimination (**49**) compounds are obtained.[42,43]



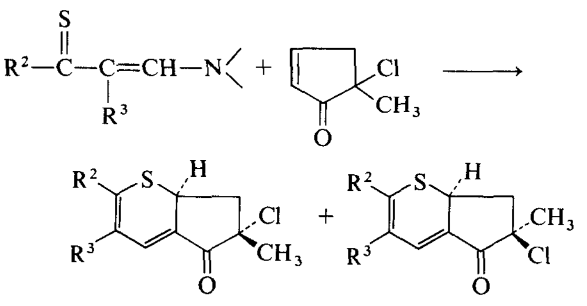
(**48**) (**49**)

The dihydrothiopyran derivatives (**48**) provide an interesting example of cis-elimination.



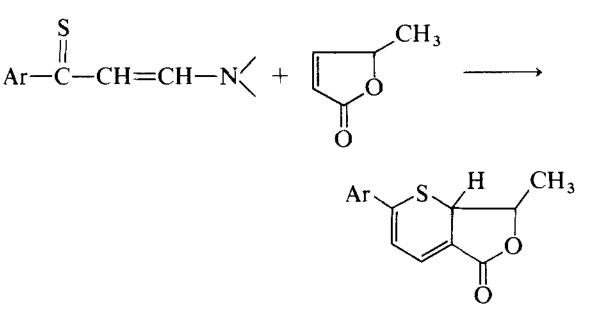
Ar = p-$CH_3OC_6H_4$

Carbocyclic compounds The substituted 5-chloro-2-cyclopentene-1-ones react with the thioamide vinylogs. Cycloaddition is followed by elimination of the amine to give the substituted 6-chloro-5, 6, 7, 7a - tetrahydro - cyclopenta - [*b*] : 5 : thiopyranones (**50**).[44]



(**50**)

Heterocyclic compounds With 2-butene-4-methyl-1,4-olide, the reaction is analogous to those above (**51**).[42]



(**51**)

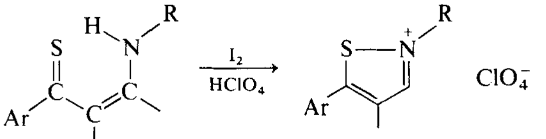
3.3 *Oxidation Reactions*

Potassium permanganate, hydrogen peroxide ... These oxidants degrade the molecule. Thus from

Ar—CS—CH=CH—N< (—N< : alkylamine)

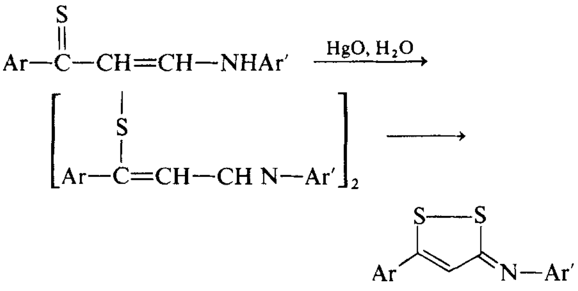
the only compound isolated is the aromatic acid Ar—COOH.[32]

Iodine Iodine oxidises the vinylogs derived from primary amines to isothiazolium salts (**52**).[26,45,46]



(**52**)

Mercuric oxide Low yields (5–10%) of the dithiole-imines are obtained, probably formed via a disulphide intermediate (**53**).[32]



(**53**)

Mercuric acetate Mercuric acetate, in acetic solution, gives low yields of the iminopropenamines (**23**) already mentioned. The amine, probably liberated by displacement by the acetate ion, reacts with the vinylog as above.[32]

4 SYNTHESIS OF THE THIOAMIDE VINYLOGS

We have divided the methods of synthesis of the thioamide vinylogs into three main categories.

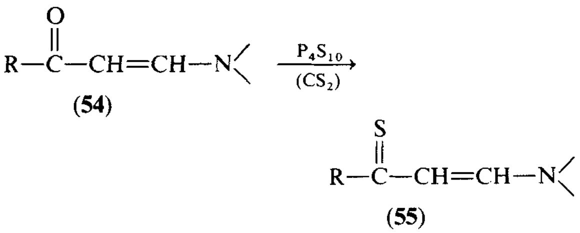
In the first category, the last reactant being brought into play introduces the sulphur atom. A carbonyl or its O-alkylated derivative is converted into a thiocarbonyl, or a carbon chloride is converted into a thiol or thiolate. The sulphur is provided by phosphorus sulphides, hydrogen sulphide, alkaline metal sulphides or cyclic dithioxodithiadiphosphetane.

In the second category, the amine reacts with an ethylenic β-mercapto-aldehyde.

The third category involves the opening of sulphur-containing rings (1,2-dithiole or isothiazole) which are usually of a cationic nature. The ring opening is effected by an amine or hydrogen sulphide.

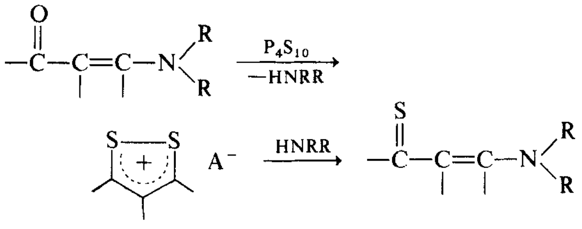
4.1

Phosphorus pentasulphide reacts with the amide vinylogs (**54**), usually dissolved or in suspension in carbon disulphide.[13,28,35,47,48]



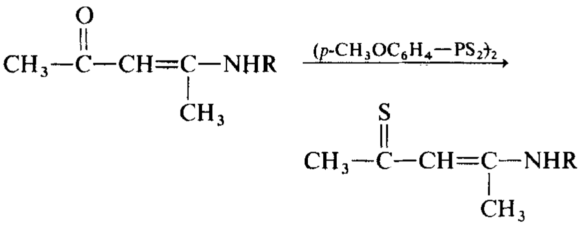
(**54**) (**55**)

For the thioamide vinylogs (**55**) derivatives of alkylamines, the reported yields are of the order of 50%. In the arylamine series, the yields, often lower than the latter, vary according to the nature of the substituents. The 1,2-dithiole-ylium salts (**56**) have been reported as reaction intermediates: the addition of the amine, at the end of the reaction, improves the yield.[49]



(56)

The use of 2,4-dithioxo-P^V, P^V-1,3,2,4-dithiadiphosphetane as a sulphurating agent was proposed recently.[50]

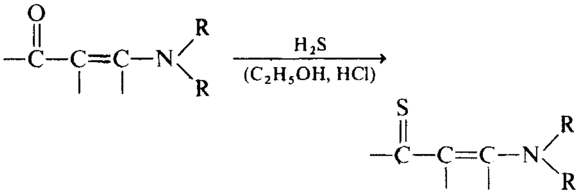


$$CH_3-\overset{O}{\overset{\|}{C}}-CH=\underset{CH_3}{\underset{|}{C}}-NHR \xrightarrow{(p\text{-}CH_3OC_6H_4-PS_2)_2} CH_3-\overset{S}{\overset{\|}{C}}-CH=\underset{CH_3}{\underset{|}{C}}-NHR$$

$R = H, C_6H_5CH_2, C_6H_4X$

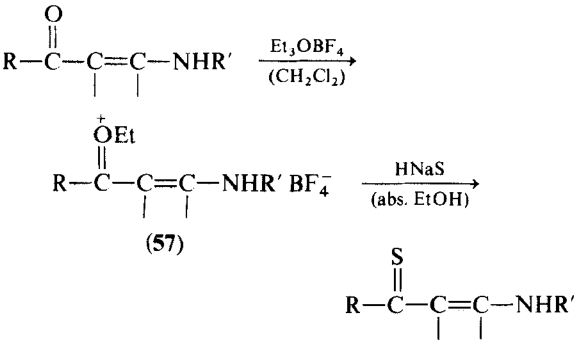
The yields obtained were between 20 and 74%.

Hydrogen sulphide reacts with the amide vinylogs, in solution in ethanol saturated with hydrogen chloride, to give the thioamides with yields less than 12% in the alkylamine series, and in the arylamine series the conversion is weak or non-existent.[29,48]



$$-\overset{O}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-NR_2 \xrightarrow[(C_2H_5OH,\ HCl)]{H_2S} -\overset{S}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-NR_2$$

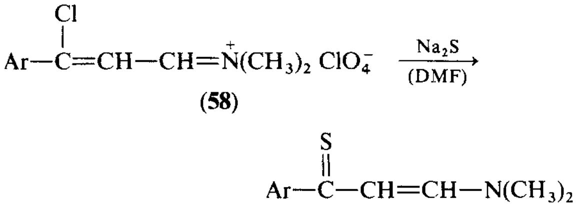
By O-alkylation of the carbonyl, via the triethyloxonium tetrafluoroborate intermediate (**57**), the electrophilic nature of carbon 1 is increased, thus improving yields (30–60%).[9,25,27]



$$R-\overset{O}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-NHR' \xrightarrow[(CH_2Cl_2)]{Et_3OBF_4} R-\overset{\overset{+}{O}Et}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-NHR'\ BF_4^- \xrightarrow[(abs.\ EtOH)]{HNaS} R-\overset{S}{\overset{\|}{C}}-\underset{|}{C}=\underset{|}{C}-NHR'$$

(57)

Good yields are also obtained by the action of the alkaline metal or ammonium sulphides on the 3-haloalkylidene-ammonium perchlorates (**58**).[51,52]



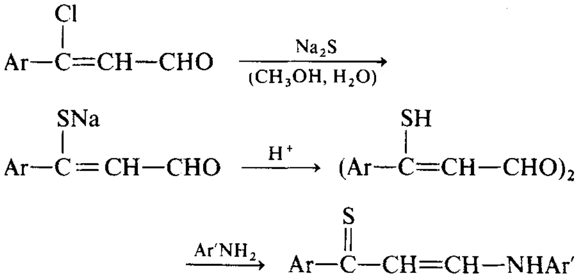
$$Ar-\overset{Cl}{\overset{|}{C}}=CH-CH=\overset{+}{N}(CH_3)_2\ ClO_4^- \xrightarrow[(DMF)]{Na_2S} Ar-\overset{S}{\overset{\|}{C}}-CH=CH-N(CH_3)_2$$

(58)

An alternative method involves reacting the salts (**58**) with sodium thiosulphate (+an amine which transaminates the salt.[53])

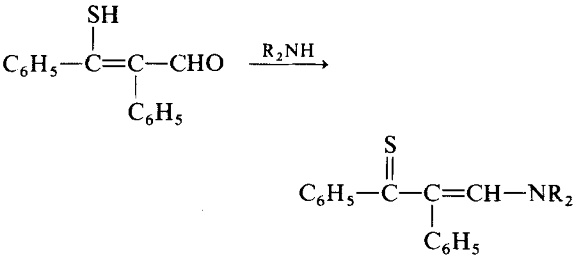
4.2

The mercapto group is attached before condensation of the amine on the aldehyde.[14,23,54]



$$Ar-\overset{Cl}{\overset{|}{C}}=CH-CHO \xrightarrow[(CH_3OH,\ H_2O)]{Na_2S} Ar-\overset{SNa}{\overset{|}{C}}=CH-CHO \xrightarrow{H^+} (Ar-\overset{SH}{\overset{|}{C}}=CH-CHO)_2 \xrightarrow{Ar'NH_2} Ar-\overset{S}{\overset{\|}{C}}-CH=CH-NHAr'$$

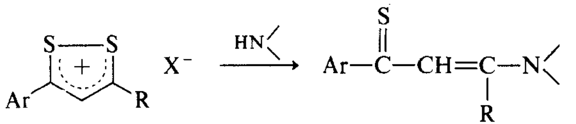
Similarly:



$$C_6H_5-\overset{SH}{\overset{|}{C}}=\underset{C_6H_5}{\underset{|}{C}}-CHO \xrightarrow{R_2NH} C_6H_5-\overset{S}{\overset{\|}{C}}-\underset{C_6H_5}{\underset{|}{C}}=CH-NR_2$$

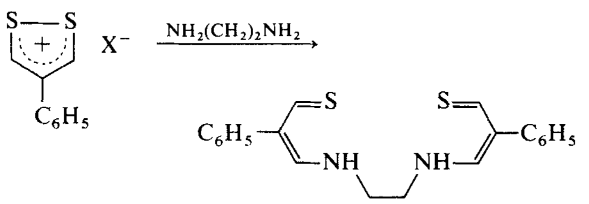
4.3

The 1,2-dithiole ylium salts, when they are easily available, are the most suitable raw materials for the synthesis of the thioamide vinylogs. The salts containing aromatic substituents have been widely used (**59**). The yields are high (up to 90%).[4,9,21,29,30,33,45–47,55]



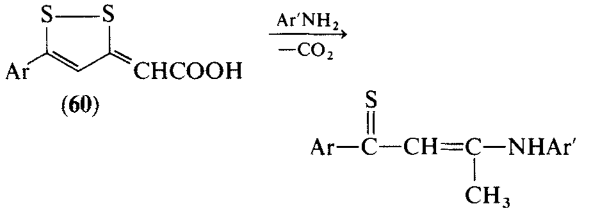
R = H, Ar

(59)



When the substituent *R* of the salt (**59**) is an aromatic group, two isomers are sometimes obtained which are difficult to separate.[49]

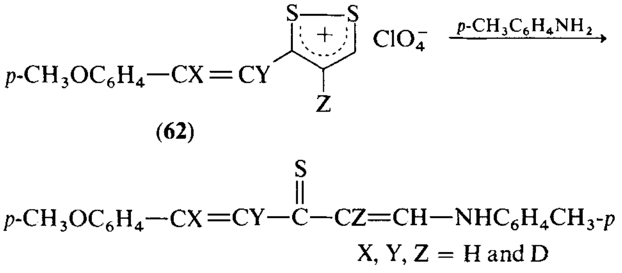
When *R* is a methyl group, it is not the expected vinylog but the product of bimolecular condensation that is obtained. The thioamide vinylog possessing a methyl group on carbon 3 (**61**) can be obtained by the sulphuration of the amide vinylog or by condensation of an amine on dithiolylidene acetic (or malonic) acid (**60**).[35]



(60)

(61)

Some deuterium derivatives of the thioamide vinylogs (**63**) have also been obtained by the opening of the 3-styryl-1,2-dithiole ylium perchlorates (**62**).[11]



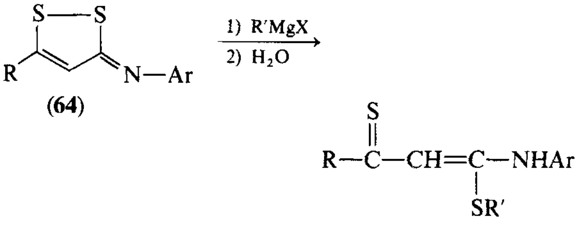
(62)

X, Y, Z = H and D

(63)

The NMR spectra of these compounds have enabled the complete interpretation of the ^1H spectra of the thioamide vinylog for which: X = Y = Z = H.

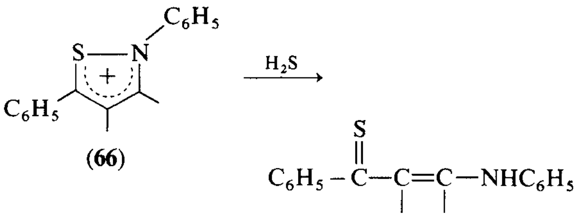
The reaction of organomagnesium compounds on the dithioleimines (**64**) gives vinylogs containing an alkylthio- or arylthiosubstituent in position 3 (**65**).[56]



(64)

(65)

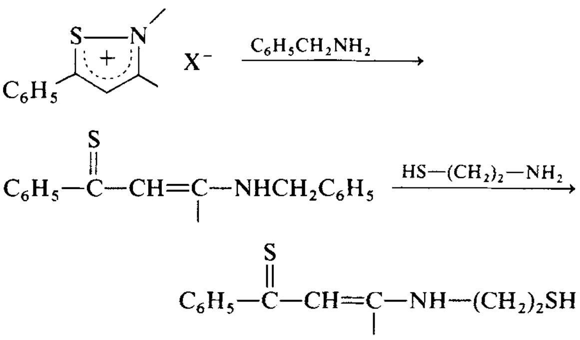
Ring closure by the oxidation of the thioamide vinylogs (NH) to isothiazolium salts has already been mentioned (*3.3*). The reduction of these salts (**66**) by hydrogen sulphide or sodium hydrosulphide regenerates the thioamide vinylogs.[57]



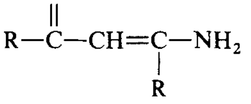
(66)

Yields range from 20 to 52%.

The opening of the isothiazolium salts may also be effected by an amine which, in this case, is substituted for the amine on the salt.[46]



It must also be remembered that the vinylogs containing no substituents on the nitrogen

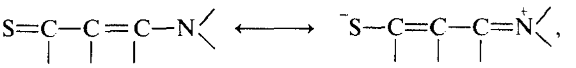


$$R-\overset{\overset{\displaystyle S}{\|}}{C}-CH=\underset{\underset{\displaystyle R}{|}}{C}-NH_2$$

can be obtained by the action of ammonia on the N-substituted vinylogs (*3.1.2*).

5 CONCLUSION

The thioamide vinylogs, stabilised by a push-pull effect between the nitrogen, an electron donor, and the thiocarbonyl, an electron acceptor:



$$S{=}\underset{|}{C}-\underset{|}{C}{=}\underset{|}{C}-N\langle \longleftrightarrow {}^{-}S-\underset{|}{C}{=}\underset{|}{C}-\underset{|}{C}{=}\overset{+}{N}\langle,$$

are more stable than the α,β-ethylenic thioketones. The thioamide vinylogs take part in numerous addition-elimination reactions as substitutes for the unknown α,β-acetylenic thioketones and also, as possible precursors of the α,β-ethylenic thioketones.

The thioamide vinylogs make up a group of extremely reactive synthetic intermediates which enable a great variety of heterocyclic compounds, often with good yields, to be obtained easily. They also have interesting chelating properties with regard to metals.

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*NOTE ADDED DURING CORRECTION OF THE PROOFS:

The reaction of 1-aryl-3-(dimethylamino)-2-propene-1-thiones with hydroxylamine-0-sulfonic acid gave also isothiazoles in 60–65% yields: Y. LIN and S. A. LANG Jr, *J. Org. Chem.*, **45**, 4857 (1980).