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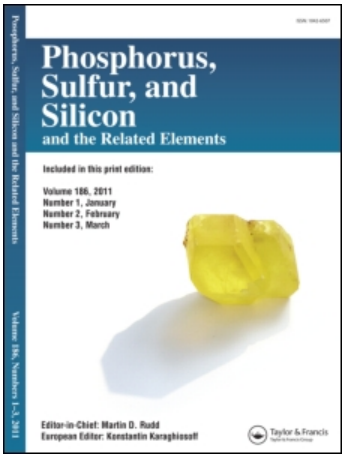

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ADDITION OF ORGANOMETALLICS ON α,β-UNSATURATED THIOCARBONYL COMPOUNDS II. MICHAEL ADDITION OF LITHIUM ENOLATES ON THIOAMIDE AND DITHIOCARBAMATE VINYLOGS AND THIOAROYLFORMAMIDINE

Jean-Pierre Guemas[a]; Michèle Lees[a]; Alain Reliquet[a]; Jean Villieras[b]
[a] Laboratoire de Chimie Organique II, NANTES Cedex, France [b] Laboratoire de Chimie Organique Physique, NANTES Cedex, France

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ADDITION OF ORGANOMETALLICS ON α,β-UNSATURATED THIOCARBONYL COMPOUNDS II. MICHAEL ADDITION OF LITHIUM ENOLATES ON THIOAMIDE AND DITHIOCARBAMATE VINYLOGS AND THIOAROYLFORMAMIDINE

JEAN-PIERRE GUEMAS†, MICHÈLE LEES†, ALAIN RELIQUET† and JEAN VILLIERAS‡

Laboratoire de Chimie Organique II,† Laboratoire de Chimie Organique Physique,‡ 2, rue de la Houssinière, 44072 NANTES Cedex (France)

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α,β-Unsaturated thiocarbonyl compounds substituted by a secondary amino group in position β, such as thioamide vinylogs, dithiocarbamate vinylogs or thioaroylformamidines react with lithium enolates of esters, ketones or amides to give 1,4-addition compounds.

In the presence of magnesium bromide 1,4-adducts undergo an intramolecular cyclization to give 2H-thiopyranones. Methylation of the 1,4-adducts is followed by a stereospecific elimination of the amine and leads to (1-Z)-1,3-dienic carbonyl compounds: with thioamide vinylogs, δ-methylthio-α,β,γ,δ-diethylenic ketones, esters and amides are obtained. Dithiocarbamate vinylogs give the α-ethylenic ketene dithioacetals, with a carbonyl function in δ-position.

Substituted dihydrothiophenes and thiazolines are prepared by the reaction of ethyl α-chloro-α-lithiopropionate with aminopropenethione and thioaroylformamidine respectively.

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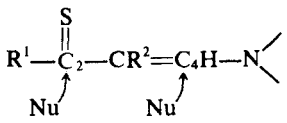
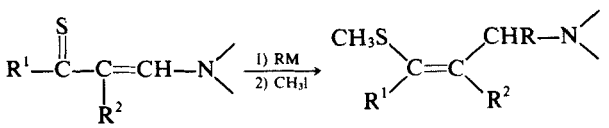
INTRODUCTION

Thioamide vinylogs **1** and dithiocarbamate vinylogs **2** are interesting and useful intermediates for the synthesis of a variety of compounds[1] as they possess reactive sites for nucleophilic attack at carbons C_2 and C_4.



1 R^1 = aryl, alkyl $R^2 = H$
2 $R^1 = CH_3S$ $R^2 = C_6H_5$

We described previously[2] the reaction of compounds **1** and **2** with organometallic reagents and we found that vinylogs of thioamides and of dithiocarbamates react with organo-magnesium and -lithium compounds selectively at carbon C_4 and the sulfur atom by a 1,4-addition. Alkylation of the 1,4-addition reaction products occurs on the sulfur and leads to α,β-ethylenic thioethers and to ketene dithioacetals.

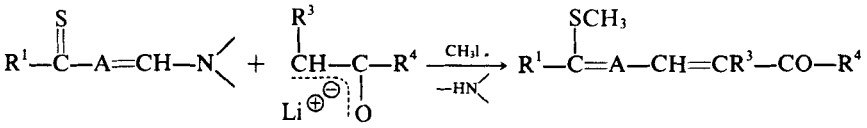


1 $R^1 = pCH_3OC_6H_4$ $R^2 = H$
2 $R^1 = CH_3S$ $R^2 = C_6H_5$

In connection with this work, we now describe the reactions of thioamide and dithiocarbamate vinylogs **1** and **2** with various lithium enolates.

The Michael reaction is very useful for the synthesis of natural products,[3] the acceptors of this condensation are generally α,β-unsaturated carbonyl compounds. Only one recent study by Tamaru, Harada and Yoshida[4] describes the use of thiocarbonyl compounds as Michael acceptors in 1,4-addition reactions of lithium enolates to α,β-unsaturated thioamides.

Owing to their instability and their great tendency to dimerize, α,β-ethylenic thioketones cannot be used in this reaction, whereas stable β-amino -α,β-ethylenic thiocarbonyl compounds and formamidines undergo the Michael condensation.



1, **2**, or **3**

1	$R^1 = p.CH_3OC_6H_4$	$A = CH$	
2	$R^1 = CH_3S$	$A = CR^2$	$R^2 = C_6H_5$
3	$R^1 = C_6H_5$	$A = N$	

Methylation of the Michael condensation products between enolates and vinylogs of thioamides **1** and of dithiocarbamates **2** is sometimes followed by the loss of the amino group and leads to various $\alpha,\beta,\gamma,\delta$-unsaturated linear carbonyl compounds, ketones and esters with a methylthio group in the δ-position.

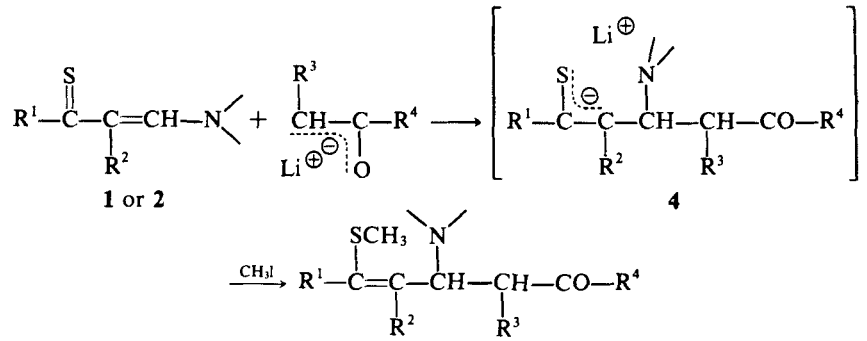
In some cases, intramolecular cyclization occurs on the 1,4-adducts to give two different types of rings, thiopyrans and thiophenes.

RESULTS AND DISCUSSION

Formation of 1,4-addition compounds

The α,β-ethylenic thiocarbonyl compounds **1** and **2** were found to react with Grignard reagents undergoing a 1,4-addition reaction[2] beginning with a nucleophilic attack at carbon C_4.

Analogous behavior is observed with various lithium enolates: vinylogs of thioamides **1** and of dithiocarbamates **2** react with enolates to give the 1,4-addition products **4**, which can be trapped as methylated compounds as shown in the following scheme:



1 or **2** **4**

1 $R^1 = p.CH_3OC_6H_4$ $R^2 = H$ $-N\!<$ = pyrrolidino, diethylamino

2 $R^1 = CH_3S$ $R^2 = C_6H_5$ $-N\!<$ = morpholino

R^3 = alkyl, aryl, H; $R^4 = (CH_3)_3CO$, C_2H_5O, $(CH_3)_2N$, C_6H_5

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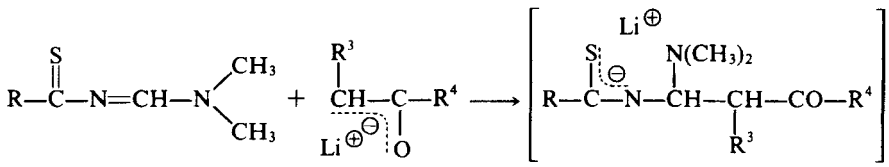
The ease of formation of the 1,4-adduct **4** of the organometallic on the thiocarbonyl substrate depends on the nature of the lithium enolate. With ester lithium enolates, tert-butyl acetate, ethyl propionate, or amide enolates, *N,N*-dimethylacetamide, the reaction occurs at a low temperature (−60°C). Increased substitution of the enolate α to the ester function greatly reduces their reactivity: with ethyl propionate the reaction is complete only when a large excess of organometallic is used; with phenyl acetate no reaction occurs.

Ketone enolates are not as reactive as the ester enolates; tert-butyl α-lithioacetate reacted rapidly at −60°C with compounds **1** and **2,** whereas α-lithiopinacolone required four hours at room temperature for total reaction. In this case the use of one equivalent of hexamethylphosphotriamide (HMPA) with respect to the ketone enolate favors a more rapid completion of the reaction. Here the reaction mixture becomes intensely colored, red, brown or purple and the disappearance of the thiocarbonyl compound must be verified by thin layer chromatography.

Similarly to the aminopropenethione **1,** *N*-thiobenzoylformamidine **3** reacts with tert-butyl acetate and pinacolone leading to the 1,4-addition compounds **5.**



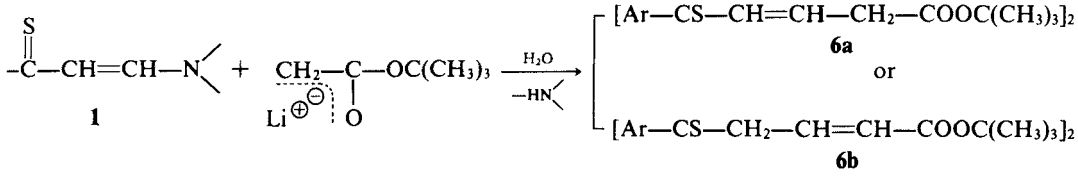
3 **5**

$R = C_6H_5$ $R_3 = H$ $R^4 = (CH_3)_3C, (CH_3)_3CO$

Hydrolysis of 1,4-adducts **4** *and* **5**

This was carried out on the products obtained by the Michael condensation of tert-butyl α-lithioacetate with compounds **1, 2** and **3.**

Here, the reaction of the thioamide vinylog **1** with tert-butyl α-lithioacetate affords, after hydrolysis, an orange oil which, according to mass spectral data (M^+ at 584), corresponds to a dimer of tert-butyl 5-*p*-methoxyphenyl-5-thioxo-2-penten- or 3-pentenoate with a yield of 75%.



1 **6a** or **6b**

$Ar = pCH_3OC_6H_4$

Further spectral data (IR, ^1H NMR) suggest a thiopyran or dithiopyran heterocycle analogous to those obtained with thiochalcones[5–7] and with α,β-ethylenic dithioesters.[8–10]

Hydrolysis of the adduct **4** obtained by the reaction of the lithium enolate of tert-butyl acetate on the dithiocarbamate vinylog **2** leads to two compounds corresponding to the replacement of the morpholino substituent by the alkyl group provided by the ester enolate. The major product **8** (yield 48%) is a dimer (m^+ 616) of the ester **7** (yield 20%) for which an analysis of the ^1H NMR spectrum, recorded in solution in deuteriochloroform, shows the two isomers E and Z (35:65).

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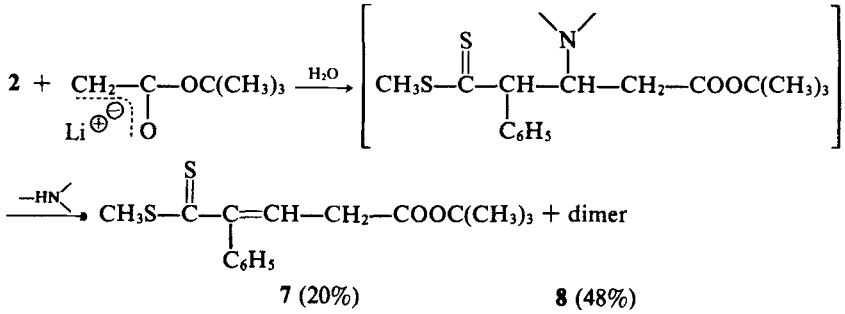
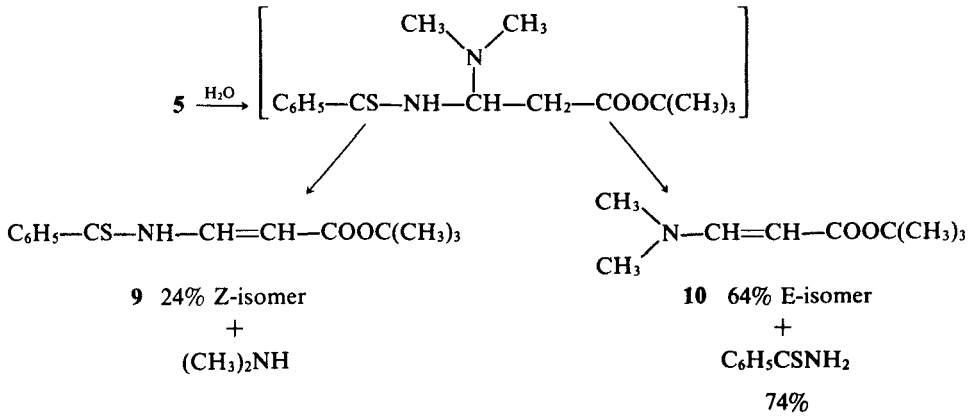


7 (20%) 8 (48%)

With thiobenzoylformamidine **3**, the reaction is different from that with the thioamide vinylogs.[2] After hydrolysis the unstable compound **5** simultaneously undergoes two types of elimination, either the elimination of dimethylamine giving rise to tert-butyl β-thiobenzamidoacrylate (yield 24%) or the elimination of thiobenzamide leading to the formation of tert-butyl *N,N*-dimethylaminoacrylate.



9 24% Z-isomer + $(CH_3)_2NH$

10 64% E-isomer + $C_6H_5CSNH_2$ 74%

The reaction between the formamidine **3** and α-lithiopinacolone afforded only 2% of the corresponding 5-thiobenzamido-4-penten-3-one (thiobenzamide was obtained in 84% yield).

Cyclization of 1,4-adducts **4** *and* **5**

The 1,4-adducts **4** and **5** contain both a nucleophilic sulfur atom and an electrophilic carbonyl group, the positions of which are favorable to an intramolecular reaction resulting in a thiopyran cyclization.

This reaction does not occur spontaneously but is brought about by the addition of anhydrous magnesium bromide. It is likely that the lithium on the sulfur atom is substituted by the bromomagnesium group, the electrophilic nature of which promotes the reaction with the carbonyl group of the ester function, so that cyclization occurs leading to the thiopyranone via elimination of an alkoxide (Scheme 1).

The best yield (63%) was obtained with 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione and tert-butyl α-lithioacetate, the 6-*p*-methoxyphenyl-thiopyran-2-one isolated was identified by comparison with a sample synthetized by another method.[11]

With ethyl propionate, the reaction affords a mixture (3:1) of 3-methyl-6-*p*-methoxyphenylthiopyran-2-one and its hemiketal with a global yield of 45%. The cyclization appears to be more difficult with the dithiocarbamate vinylog **2**: the thio-

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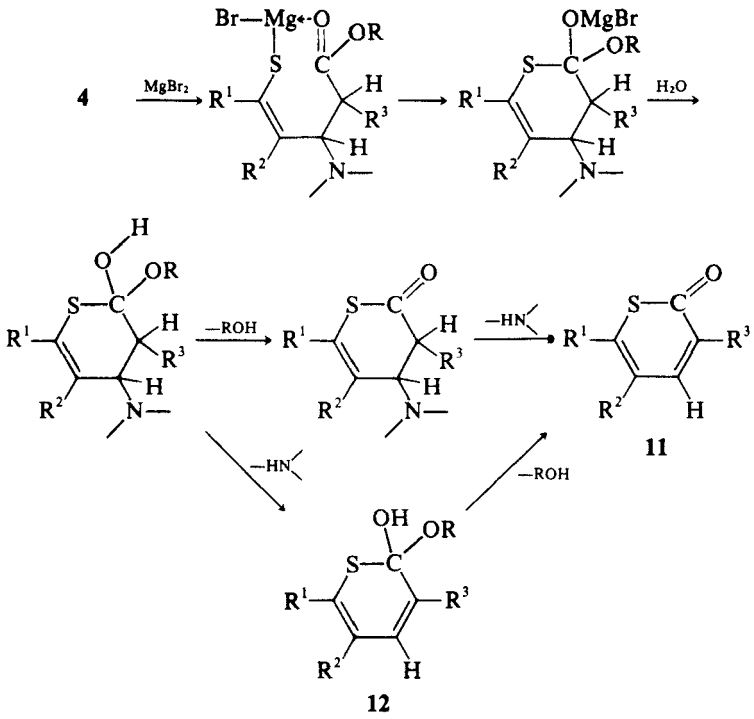


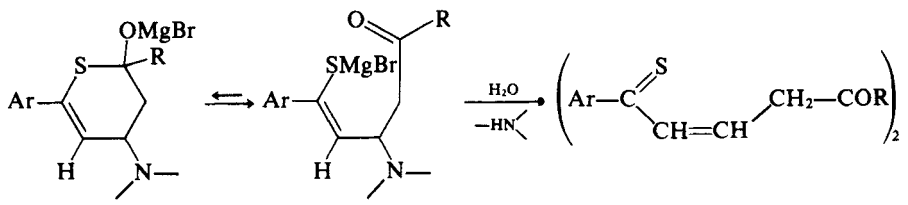
$R^1 = pCH_3OC_6H_4$	$R^2 = H$	$R^3 = H$	yield	63% of **11a**
$R^1 = pCH_3OC_6H_4$	$R^2 = H$	$R^3 = CH_3$	global yield	45% of **11b** and **12b**
$R^1 = CH_3S$	$R^2 = C_6H_5$	$R^3 = H$	yield	26% of **11c**

Scheme 1

pyrannic heterocycle was obtained in only 26% yield, in the presence of magnesium dibromide.

This type of cyclization, applied to *N*-thioaroylformamidine **3** is interesting because it would lead to 1,3-thiazines, which can be considered as precursors of cephems and cephalosporins.[12] Unfortunately, the addition of magnesium bromide after the formation of the 1,4-adduct **5** did not alter the course of the reaction, the only isolated products, thiobenzamide and *N,N*-dimethylacrylate, correspond to those obtained by hydrolysis.

In spite of some experiments carried out in various conditions with aminopropenethione **1** and α-lithiopinacolone, no products were obtained which correspond to an intramolecular cyclization. The magnesium salt of the monothiohemiketal cannot be stabilized by elimination as in the case of the esters and is probably less stable than the initial 1,4-adduct, which is obtained finally after hydrolysis as its dimer.[13]



$Ar = pCH_3OC_6H_4$

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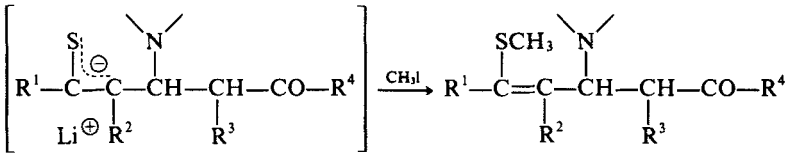
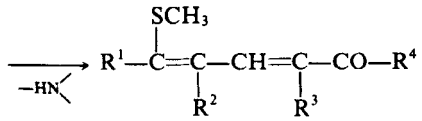
Methylation of 1,4-addition compounds **4**

Methylation of the 1,4-adduct **4** occurs at the sulfur atom and, unlike hydrolysis, affords stable products of the initial Michael reaction.



4 **13** or **15**



14 or **16**

The alkylation reaction is carried out at room temperature using excess iodomethane; a change in color (to yellow) of the reaction mixture is observed.

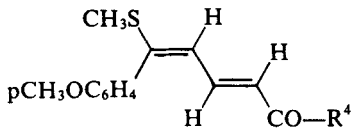
According to the nature of the lithium enolate, the reaction can be followed by a loss of the amino group, pyrrolidino or diethylamino for the thioamide vinylogs and morpholino for the dithiocarbamate vinylogs.

With the enolates of tert-butylacetate, ethyl propionate or *N,N*-dimethylacetamide, the amino compounds **13** are sufficiently stable to be isolated. On the contrary with ketone enolates such as pinacolone, methyl isopropyl ketone and acetophenone, the amino substituent is spontaneously eliminated and $\alpha,\beta,\gamma,\delta$-unsaturated ketones with a methylthio group in the δ-position are obtained. The α,γ-diethylenic esters **14** (R^4 = tert-butoxy, ethoxy) can be prepared from compounds **13** by the quaternization of the amine with methyl iodide as solvent and reagent, and then refluxing for a few hours in benzene in the presence of pyridine as base.

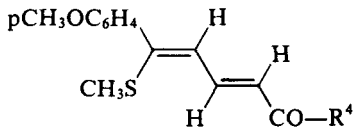
Results and experimental conditions are summarized in two tables, Table I for the compounds prepared from aminopropenethiones **1** and Table II for the ketene dithioacetals **15** and **16.**

The structure of products **14** was determined from proton nuclear magnetic resonance spectral data.

Theoretically, in view of the two double bonds, four isomeric structures EE, ZZ, EZ and ZE are expected. Examination of the NMR signals of the ethylenic protons, shows that only two isomers of **14** were prepared: the larger spin-spin coupling constant of about 15 Hz, indicates an E-isomeric form for the double bond next to the carbonyl function; the value of J = 11 Hz for the protons attached to the carbon–carbon single bond is in favor of a s-trans conformation.



s-trans E,E **14**



s-trans Z,E **14**

For the methylthio group, two different signals were observed at 1.97 ppm and 2.28 ppm, for the Z and E isomers respectively, with a predominance, about 80%, for the Z-isomer in all cases except with pinacolone where the ratio is inversed.

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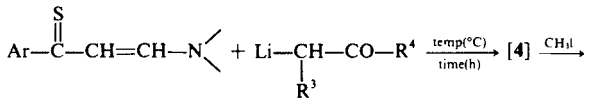
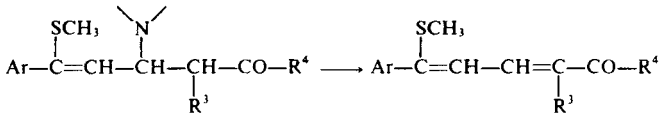
TABLE I

Methylation of 1,4-addition compounds of lithium enolates on thioamide vinylogs **1**.



1



13 **14**

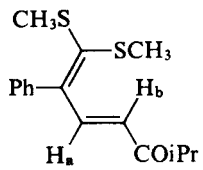
Ar = $pCH_3OC_6H_4$

Compound	$-N_{\diagup}^{\diagdown}$	R^3	R^4	temperature[a] (°C)	time[a] (h)	compound **13** yield (%)	compound **14** yield (%)
a	$N(Et)_2$	H	tBuO	−60	1	76	57(75)[b]
b	$N(Et)_2$	Me	EtO	−60	1	58[c]	36(40)[b]
	$N(Et)_2$	Ph	EtO	20	12	no reaction	
c	N⟨ ⟩	H	$(Me)_2N$	−60	1	not isolated	21[e]
d	$N(Et)_2$	H	iPr	20	4[d]	not isolated	77[e]
e	N⟨ ⟩	H	tBu	20	4[d]	not isolated	90[e]
f	$N(Et)_2$	H	Ph	20	3[d]	not isolated	89[e]

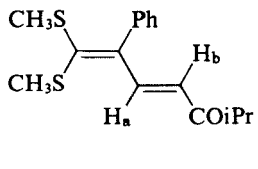
[a] Experimental conditions for the formation of **4**.
[b] Yield calculated from compound **13**.
[c] Incomplete reaction, 35% of **1** were recovered.
[d] HMPA (one equivalent/enolate) was added.
[e] Obtained directly without isolating **13**.

This result differs from that obtained from the reaction of Grignard reagents on thioamides vinylogs, where the 1,4-addition was stereospecific and afforded only the Z-isomer. Here the methylthio group can occupy the two positions corresponding to the Z- and E-isomers, while the two hydrogen atoms of the middle double-bond are trans, so only the elimination of the amine is stereospecific.

From the ^1H NMR study of the α,β-ethylenic ketenedithioacetals **16**, a value of about 15 Hz for the spin–spin coupling constant of the ethylenic protons shows that they are (E)-related.



s-cis **16**



s-trans **16**

Because of the two conjugated carbon–carbon double bonds, compounds **16** may exist in the s-cis or/and s-trans conformations: to determine which of these is the preferential conformation, irradiation at 1000 Hz was carried out on both methylthio groups of compound **16**, but no appreciable Overhauser effect was detected on the ethylenic protons H_a and H_b.

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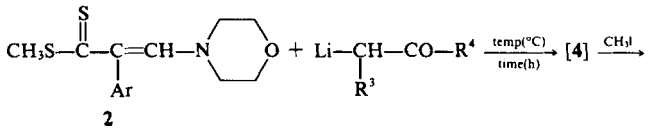
TABLE II

Methylation of 1,4-addition compounds of lithium enolates on dithiocarbamate vinylogs **2**



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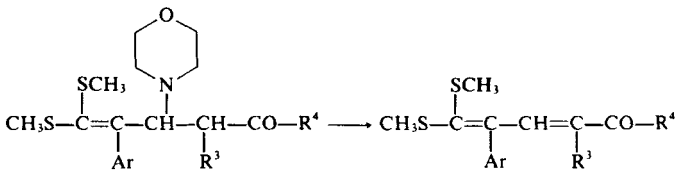


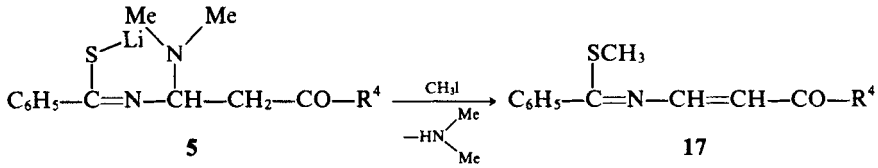
15 **16**

Ar = Phényl

Compound	R^3	R^4	temperature[a] (°C)	time[a] (h)	compound **15** yield (%)	compound **16** yield (%)
a	H	tBuO	−50	3	78	70(89)[b]
b	Me	EtO	−50	3	85	
	Ph	EtO	20	20	no reaction	
c	H	$(Me)_2N$	−50	3	86	40(47)[b]
d	H	iPr	20	20[c]	not isolated	40
e	H	tBu	20	20[c]	not isolated	46
f	H	Ph	20	20[c]	not isolated	67

[a] Experimental conditions for the formation of **4**.
[b] Yield calculated from compound **15**.
[c] No HMPA was added.

Alkylation of the 1,4-addition compound **5** prepared by the action of lithium enolates of *t*-butyl acetate and pinacolone on the *N*-thioaroylformamidine also occurs on the sulfur atom, the yield being lower, in particular with pinacolone (6%). Moreover, the major product in this case, *N,N*-dimethylaminoacrylate, arises from the hydrolysis of **5**.



5 **17**

R^4 = tBuO Yield = 38% (Z isomer only)

R^4 = tBu Yield = 6% (Z isomer only)

The alkylation reaction can be used in the synthesis of five-membered heterocycles by reacting the thiocarbonyl substrates **1** or **3** with α-chlorinated enolates. The 1,4-adduct **4** or **5** formed by condensation of ethyl α-chloro-α-lithiopropionate on the α,β-unsaturated thiocarbonyl compounds **1** or **3** spontaneously undergoes an intramolecular cyclization different to that observed in the presence of magnesium bromide. In this case, the chlorine atom is substituted by the sulfur atom via a nucleophilic attack of the thiolate anion leading to the five-membered heterocycles (Scheme 2).

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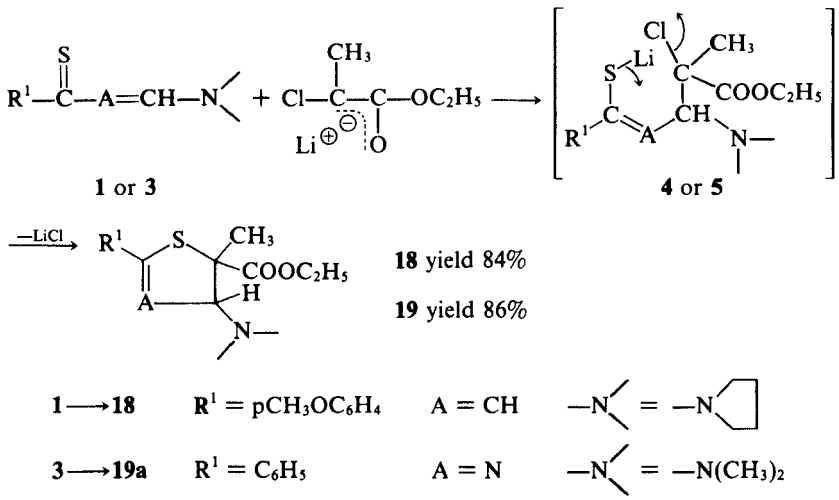
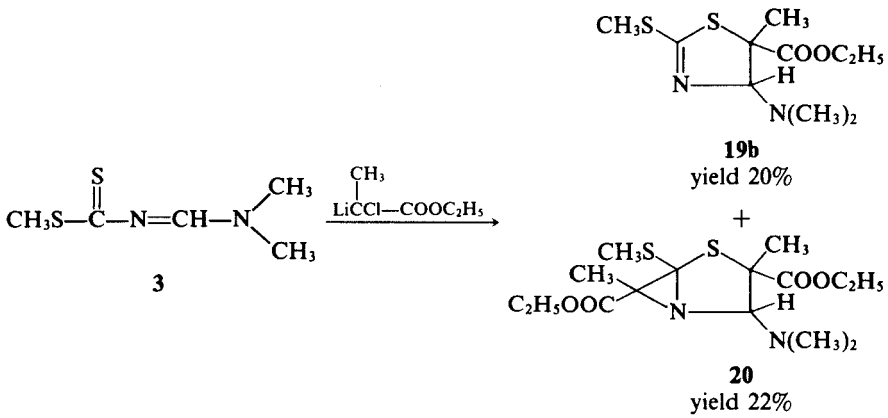


SCHEME 2

The addition of the lithium enolate of ethyl α-chloropropionate on 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione **1** and on N^1,N^1-dimethyl-N^2—thiobenzoylformamidine **3** is carried out at a low temperature (−50°C), and then allowed to warm to room temperature for the cyclization to take place. The corresponding dihydrothiophene **18** and dihydrothiazole **19** are obtained in good yields, 84% and 86%. Further experiments with the lithium enolate of ethyl chloracetate were unsuccessful.

The vinylog of dithiocarbamate **2** did not react with the α-chlorinated enolate of ethyl propionate and was recovered.

With formamidine **3** ($R^1 = CH_3S$) double addition of the enolate is observed and two products are isolated:



One was the expected 2-methylthio-1,3-thiazoline corresponding to a 1,4-addition and cyclization as described above. In the second, the excess organometallic adds on the imine double-bond of the formed thiazole (probably via a carbenoïd insertion on the imine double-bond) to form an aziridine ring fused on the thiazolidine system.[14]

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EXPERIMENTAL

^{1}H NMR spectra were measured using a Perkin-Elmer R 24 spectrometer or Varian XL 100 spectrometer in deuteriochloroform as solvent with tetramethylsilane as internal standard. Chemical shifts are reported as δ values in parts per million relative to the internal standard.

Mass spectra were determined with a Varian MAT 112 spectrometer at 70 eV.

The purity of compounds was tested by thin layer chromatography on silica gel plates developed with iodine vapor. Melting points are reported in degrees Celsius and are uncorrected. Elemental analyses were performed by the Central Service of Microanalysis of the C.N.R.S., Thiais, France.

All reactions between lithium enolates and thiocarbonyl compounds were carried out under an atmosphere of dry nitrogen.

Tetrahydrofuran (THF) was dried over a mixture of naphthalene sodium, distilled and stored under nitrogen over molecular sieves. Diethylether was dried over calcium chloride, then sodium. *n*-Butyllithium in hexane was obtained from Aldrich and titrated before use.[15]

Preparation of starting materials **1, 2** *and* **3:**

3-Dialkylamino-1-*p*-methoxyphenyl-2-propen-1-thiones **1** were prepared by the action of diethylamine or pyrrolidine on 3-aryl-1,2-dithiolylium salts.[16]

Methyl 3-morpholino-2-phenyl-2-propen-dithioate **2** was prepared according to Smutny[17] by the reaction of morpholine on 4-aryl-3-methylthio-1,2-dithiolylium iodide.

The procedure of Weidinger and Eilingsfeld[18] was used to prepare N^1,N^1-dimethyl-N^2-thiobenzoylformamidine **3** by condensation of dimethylformamide diethyl acetal on thiobenzamide.

Preparation of 1,4-addition compounds **4** *and* **5.** *General procedure*

The ester, ketone or amide α-lithioenolate was prepared at −80°C, in a flame-dried 500 mL round-bottomed flask, equipped with a magnetic stirrer, a low temperature thermometer (−100°C, +50°C) and a pressure-equalizing addition funnel, by the addition of the carbonyl compound in a THF solution (10 mmol in 8 mL of dry THF) to 10.2 equivalents of lithium diisopropylamide (LDA).

After stirring for 40 min at −80°C, a THF solution of the appropriate thiocarbonyl compound **1, 2** or **3** (4 mmol in 20–30 mL of dry THF) was added dropwise. The reaction mixture was then stirred at the temperature and for the length of time indicated in Tables I and II.

With the enolates of esters and *N,N*-dimethylacetamide, the initial color of the thiocarbonyl compound disappeared slowly to give a light-colored reaction mixture.

With the enolates of ketones, pinacolone, isopropyl methyl ketone and acetophenone, the condensation was performed at room temperature for a longer time and in the presence of hexamethylenephosphotriamide (HMPA), which was introduced in an equivalent amount with respect to the ketoenolate before the addition of the thiocarbonyl compound. The reaction mixture became dark red or dark purple; the reaction was followed by TLC analysis which showed the disappearance of the starting product **1, 2** or **3.**

Dimer of tert-butyl 5-p-*methoxyphenyl-5-thioxo-3-pentenoate* **6**

The addition of tert-butyl α-lithioacetate on 3-diethylamino-1-*p*-methoxyphenyl-2-propen-1-thione **1** was carried out at −70°C as described above. The colorless suspension of the 1,4-adduct **4** was allowed to warm to room temperature for 2 h, after which a red suspension similar to that of the thioxoenamine was obtained.

After cooling to −70°C, the hydrolysis was performed rapidly by the addition of a saturated aqueous solution of ammonium chloride. After warming to room temperature, the aqueous THF solution was extracted three times with 100 mL portions of benzene. The benzene extracts were combined, washed with water, dried (Na_2SO_4) and concentrated in vacuo. The resulting crude product, an orange oil, was chromatographed on a silica gel column; elution with benzene-ethyl acetate (9:1) gave 0.88 g (75%) of a yellow oil of dimer **6.** Attempted purification of this oil by recrystallization was unsuccessful; ^{1}H NMR ($CDCl_3$) δ, 1.47 (m, 18H, $(CH_3)_3C$), 2.40–2.60 (m, 4H, CH_2), 3.80 (2s, 6H, CH_3O), 5.8–6.0 (m, 2H, —CH=), 6.77–7.67 (m, 10H, aromatics and ethylenics); mass spectrum, m/e 584 (m^+).

Hydrolysis of 1,4-adduct **4** *prepared from methyl 3-morpholino-2-phenyl-2-propenedithioate* **2**

Methyl 3-morpholino-2-phenyl-2-propenedithioate **2** was condensed on tert-butyl α-lithioacetate at −50°C as described above in the general procedure. Hydrolysis and isolation of the resulting crude products were performed as for compound **6.**

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The mixture was chromatographed on a silica gel column; elution with benzene and then with a mixture of benzene-diethyl ether (20:1) gave two products: 0.4 g of a red oil corresponding to the monomer **7** (yield 20%) and 0.57 g (48%) of yellow crystals of dimer **8**.

Tert-butyl 4-[(methylthio)thiocarbonyl]-4-phenyl-3-butenoate **7:** unstable red oil characterized by ^{1}H NMR ($CDCl_3$) isomer Z δ 1.42 (s, 9H, $(CH_3)_3C$), 2.54 (s, 3H, CH_3S), 2.90 (d, J = 7.3 Hz, 2H, CH_2), 7.02 (t, J = 7.3 Hz, H, =CH); isomer E 1.56 (s, 9H, $(CH_3)_3C$), 2.64 (s, 3H, CH_3S), 3.18 (d, J = 7.3 Hz, 2H, CH_2), 6.12 (t, J = 7.3 Hz, H, =CH); mass spectrum m/e 308 (m^+).

Dimer **8:** yellow crystals, mp 124–128°C (hexane); mass spectrum, m/e 616 (m^+). Anal. Calcd for $C_{32}H_{40}O_4S_4$: C, 62.30; H, 6.54; S, 20.79. Found C, 62.46; H, 6.48; S, 20.36.

Hydrolysis of 1,4-adduct **5** *prepared from* N^1,N^1*-dimethyl-*N^2*-thiobenzoylformamidine* **3** *with tert-butyl acetate lithium enolate*

N^1,N^1-dimethyl-N^2-thiobenzoylformamidine **3** (0.77 g, 4 mmol) reacted completely at −70°C in 30 min with the α-lithioenolate of tert-butyl acetate according to the general procedure described above.

After complete discoloration of the reaction mixture, the hydrolysis was carried out by the rapid addition of a saturated aqueous solution of ammonium chloride. After extraction with benzene the products were separated by chromatography on an alumina column: elution with benzene afforded 0.25 g (24%) of tert-butyl (Z)-β-thiobenzamidoacrylate **9** as orange crystals mp 76–78°C (hexane); ^{1}H NMR ($CDCl_3$) δ 5.26 (d, J_1 = 9.0 Hz, H, =CH—CO), 8.17 (2d, J_1 = 9.0 Hz and J_2 = 9.0 Hz, H, =CH—N), 12.17 (bd, J_2 = 9.0 Hz, H, NH); mass spectrum, m/e 263 (m^+). Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32; S, 12.18. Found C, 63.94; H, 6.61; N, 5.31; S, 12.09. Elution with benzene-diethyl ether (9:1) gave 0.53 g (74%) of thiobenzamide as yellow crystals mp 115–116°C (ethanol) and 0.57 g (64%) of the tert-butyl (E)-β-dimethylaminoacrylate[19] **10** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 4.33 (d, J = 12.8 Hz, H, =CH—CO), 7.23 (d, J = 12.8 Hz, H, =CH—N); mass spectrum, m/e 171 (m^+).

Hydrolysis of 1,4-adduct **5** *prepared from* N^1,N^1*-dimethyl-*N^2*-thiobenzoylformamidine* **3** *with pinacolone lithium enolate*

N^1,N^1-dimethyl-N^2-thiobenzoylformamidine **3** (0.77 g, 4 mmol.) was alkylated using α-lithiopinacolone according to the general procedure. After hydrolysis and extraction with benzene, chromatography on a silica gel column gave, after elution with benzene, only 20 mg (2%) of *N*-(4,4-dimethyl-3-oxo-1-penten-1-yl)-thiobenzamide as a light yellow oil; ^{1}H NMR ($CDCl_3$) δ 6.0 (d, J_1 = 9 Hz, H, =CH—CO), 8.22 (2d, J_1 = 9 Hz and J_2 = 9 Hz, H, CH—N), 13.4 (bd, J_2 = 9 Hz, H, HN); mass spectrum m/e 247 (m^+). Elution with benzene-diethyl ether (9:1) afforded 0.46 g (84%) of thiobenzamide and 0.15 g (24%) of 1-dimethylamino-4,4-dimethyl-1-penten-3-one[20] as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 5.20 (d, J = 12 Hz, H, =CH—CO), 7.53 (d, J = 12 Hz, H, =CH—N); mass spectrum m/e 155 (m^+).

Cyclization of 1,4-adduct **4:** *6-*p*-methoxyphenyl-2H-thiopyran-2-one* **11a**

The general procedure described above was used to prepare the 1,4-adduct **3** resulting from the addition of tert-butyl α-lithioacetate on the 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione **1.** After the addition, the reaction mixture was allowed to warm to −50°C while stirring until complete discoloration. To the resulting mixture was added a solution of 10 mmol of magnesium dibromide in 10 mL of dry diethyl ether, prepared before use from 0.27 g (11 mmol) of magnesium and 1.88 g (10 mmol) of 1,2-dibromoethane. The reaction mixture was stirred at −50°C for 30 min and then at room temperature overnight. The red solution obtained was cooled to −80°C and hydrolyzed by the addition of 100 mL of saturated ammonium chloride aqueous solution.

The aqueous THF solution was extracted three times with 50 mL portions of benzene. The benzene extracts were combined, washed with water saturated by sodium chloride, decanted, dried (Na_2SO_4) and concentrated in vacuo to give the crude product, which was purified by chromatography on an alumina column. Elution with benzene gave a yellow solid, 0.55 g (63%), which was recrystallized from ethanol to give 6-*p*-methoxyphenyl-2H-thiopyran-2-one **11**[11] mp 119–120°C: ^{1}H NMR ($CDCl_3$) δ 6.37 (d, J_1 = 10 Hz, H, =CH—CO), 6.90 (d, J_2 = 7.5 Hz, H, =CH—CS), 7.40 (dd, J_1 = 10 Hz and J_2 = 7.5 Hz, H, CH—CH=CH); mass spectrum m/e 218 (m^+).

Cyclization of 1,4-adduct **4:** *6-*p*-methoxyphenyl-3-methyl-2H-thiopyran-2-one* **11b** *and 2-ethoxy-2-hydroxy-6-*p*-methoxyphenyl-3-methyl-2H-thiopyran* **12b**

Ethyl α-lithiopropionate was condensed on the 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione **1** and the cyclization using magnesium bromide was carried out as for compound **11a.** After extraction

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and concentration in vacuo, the resulting red oil was chromatographed on an alumina column: elution with benzene gave 0.45 g of a mixture† (6:4) of **11b** and **12b**, and by elution with benzene-ethyl acetate (9:1), 0.30 g of the thioxoenamine **1** were recovered. A second chromatography on an alumina column of the previous mixture of **11b** and **12b** gave with benzene as eluent, 0.10 g of the **11b** as yellow crystals mp 110–120°C (cyclohexane); ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H, CH_3), 6.83 (d, J_1 = 7.5 Hz, H, =CH—CS), 7.30 (d, J_1 = 7.5 Hz, H, =CH—CCH_3); mass spectrum m/e 232 (m^+). Compound **12b** non-isolated, ^{1}H NMR, in solution with **12a** in $CDCl_3$ visible by δ 1.03 (t, J = 7 Hz, 3H, CH_3—CH_2), 1.97 (s, 3H, CH_3), 4.03 (q, J = 7 Hz, 2H, CH_2—CH_3).

Cyclization of 1,4-adduct **4**: *6-methylthio-5-phenyl-2H-thiopyran-2-one* **11c**

This was carried out following the procedure described for compound **11a** using dithiocarbamate vinylog **2** and tert-butyl acetate α-lithioenolate. The resulting crude product was chromatographed twice on a silica gel column using a mixture of benzene-petroleum ether as eluent, to give 0.24 g (26%) of **11c** as orange crystals mp 79–81°C (hexane) (mp 80–82 in the literature[21]); ^{1}H NMR ($CDCl_3$) δ 6.22 (d, J = 10 Hz, H, =CH—CO), 7.17 (d, J = 10 Hz, H, =CH—$C(C_6H_5)$); mass spectrum m/e 234 (m^+).

Methylation of 1,4-adduct **4**

The 1,4-adduct **4** (4 mmol) was prepared from the thioamide vinylog **1** (or from the dithiocarbamate vinylog **2**) following the general procedure described above. The alkylation was carried out by the addition, at the same temperature (Tables I and II), of 2.28 g of methyl iodide (16 mmol in 5 mL of dry THF). After warming to room temperature, the reaction mixture was stirred for 2 h, at the end of which it became yellow or orange.

Hydrolysis and extraction were performed as for compound **6**. After removing the solvents in vacuo, the resulting orange or red oil was then chromatographed on an alumina column. Elution with benzene gave compound **13, 14, 15** or **16**. Yields are given in Table I for compounds **13** and **14**, and in Table II for compounds **15** and **16**.

Attempted purification of compounds **13a, 13b, 14c, 14d, 14c, 14f, 15b, 15c, 16a** by crystallization was unsuccessful, these compounds were isolated as unstable oils, for which the structures were determined on the basis of their ^{1}H NMR and mass spectra.

*Tert-butyl 3-diethylamino-5-*p*-methoxyphenyl-5-methylthio-4-pentenoate* **13a**: orange oil, ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3S), 2.43 (m, masked CH_2), 4.50 (dt, J = 9.7 Hz, H, CH), 5.75 (d, J = 9.7 Hz, H, =CH); mass spectrum m/e 379 (m^+).

*Ethyl 3-diethylamino-2-methyl-5-*p*-methoxyphenyl-5-methylthio-4-pentenoate* **13b**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3H, CH_3S), 2.50 (m, masked CH—CH_3), 4.0 (m, masked CH—N), 5.80 (d, J = 9.7 Hz, H, =CH); mass spectrum m/e 364 (m^+).

N,N-*Dimethyl-5-*p*-methoxyphenyl-5-methylthio-2,4-pentadienamide* **14c**: colorless oil, ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H, CH_3S), 6.05–6.45 (m, 2H, ethylenics), 7.06–7.38 (m, ethylenic masked by aromatics); mass spectrum m/e 277 (m^+).

*7-*p*-Methoxyphenyl-2-methyl-7-methylthio-4,6-heptadien-3-one* **14d**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 1.96 and 2.27 (2s, 3H, CH_3S) Z-isomer 77% and E-isomer 23%, 3.73 (s, 3H, CH_3S), 6.26 (d, J = 14.3 Hz, H, =CH—CO), 6.43 (d, J = 11 Hz, H, =CH), 7.93 (dd, J = 11 Hz and J = 14.3 Hz, H, CH—CH=CH); mass spectrum m/e 276 (m^+).

*7-*p*-Methoxyphenyl-2,2-dimethyl-7-methylthio-4,6-heptadien-3-one* **14e**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 1.99 and 2.28 (2s, 3H, CH_3S) Z-isomer 86% and E-isomer 14%, 6.50 (d, J = 11.2 Hz, H, =CH), 6.61 (d, J = 14.8 Hz, H, =CH), 8.05 (dd, J = 11.2 Hz and J = 14.8 Hz, CH—CH=CH—); mass spectrum m/e 290 (m^+).

*5-*p*-Methoxyphenyl-5-methylthio-1-phenyl-2,4-pentadien-1-one* **14f**: yellow oil, ^{1}H NMR ($CDCl_3$) δ 1.93 and 2.23 (2s, 3H, CH_3S) Z-isomer 67% and E-isomer 33%, 6.27 (d, J = 11.2 Hz, H, =CH), 6.60

†The ratio was determined by analysis of the ^{1}H NMR spectra on the basis of the methyl proton signal.

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(masked ethylenic), 9.27 (dd, J = 11.2 Hz and J = 14.7 Hz, H, CH—CH=CH); mass spectrum, m/e 310 (m^+).

Tert-butyl 5,5-bis(methylthio)-3-morpholino-4-phenyl-4-pentenoate **15a:** white crystals, mp 84–88°C (hexane), ^1H NMR ($CDCl_3$) δ 2.15 and 2.32 (2s, 6H, CH_3S), 2.22 (d, J = 7.2 Hz, 2H, CH_2), 4.78 (t, J = 7.2 Hz, H, CH); mass spectrum m/e 409 (m^+). Anal. Calcd. for $C_{21}H_{31}NO_3S_2$: C, 61.57; H, 7.63. Found: C, 61.75; H, 7.61.

Ethyl 2-methyl-5,5-bis(methylthio)-3-morpholino-4-phenyl-4-pentenoate **15b:** colorless oil, ^1H NMR ($CDCl_3$) δ 2.10 and 2.33 (2s, 6H, CH_3S), 2.22 (d, J = 10 Hz, 3H, CH_3—CH), 3.03 (m, H, CH—CH_3), 4.15 (masked CH), 4.90 (d, J = 11 Hz, H, CH); mass spectrum m/e 395 (m^+).

N,N-*Dimethyl-5,5-bis(methylthio)-3-morpholino-4-phenyl-4-pentenamide* **15c:** pale yellow oil, ^1H NMR ($CDCl_3$) δ 2.17 and 2.32 (2s, 6H, CH_3S), 2.20 (d, J = 7 Hz, 2H, CH_2), 4.75 (t, J = 7 Hz, H, CH); mass spectrum m/e 381 (m^+).

2-Methyl-7,7-bis(methylthio)-6-phenyl-4,6-heptadien-3-one **16d:** white crystals, mp 59–60°C (hexane), ^1H NMR ($CDCl_3$) δ 2.20 and 2.38 (2s, 6H, CH_3S), 5.63 (d, J = 15 Hz, H, =CH), 8.30 (d, J = 15 Hz, H, =CH); mass spectrum m/e 292 (m^+). Anal. Calcd. for $C_{16}H_{20}OS_2$: C, 65.70; H, 6.89; S, 21.99. Found: C, 65.64; H, 6.91; S, 21.99.

2,2-Dimethyl-7,7-bis(methylthio)-6-phenyl-4,6-heptadien-3-one **16e:** yellow crystals, mp 63–65°C (hexane), ^1H NMR ($CDCl_3$) δ 2.18 and 2.38 (2s, 6H, CH_3S), 6.04 (d, J = 15 Hz, H, =CH), 8.46 (d, J = 15 Hz, H, =CH); mass spectrum m/e 306 (m^+). Anal. Calcd. for $C_{17}H_{22}OS_2$: C, 66.62; H, 7.24; S, 20.92. Found: C, 66.73; H, 7.28; S, 21.01.

5,5-Bis(methylthio)-1,4-diphenyl-2,4-pentadien-1-one **16f:** yellow crystals, mp 103–104°C (EtOH), ^1H NMR ($CDCl_3$) δ 2.22 and 2.40 (2s, 6H, CH_3S), 6.46 (d, J = 16.4 Hz, H, =CH), 8.53 (d, J = 16.4 Hz, H, =CH); mass spectrum m/e 326 (m^+). Anal. Calcd. for $C_{19}H_{18}OS_2$: C, 69.90; H, 5.56. Found: C, 69.58; H, 5.68.

Preparation of compounds **14** *from compounds* **13**

*Tert-butyl 5-*p*-methoxyphenyl-5-methylthio-2,4-pentadienoate* **14a:** 1.16 g (3.06 mmol) of compound **13a** prepared from 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione **1** and tert-butyl α-lithioacetate was dissolved in pure methyl iodide (10 mL) and stirred overnight. After removing the iodomethane in vacuo, the resulting viscous residue was stirred in 25 mL of a mixture of benzene-pyridine (4:1) for 1 h and heated under reflux for 12 h. After cooling, the benzene solution was washed with HCl 5% aqueous solution to remove the pyridine, then with water, decanted, dried (Na_2SO_4) and concentrated under reduced pressure.

Chromatography on an alumina column of the light yellow oil obtained gave, by elution with a mixture benzene-petroleum ether (1:1), 0.70 g, yield 57% (25% of **1** were recovered) of compound **14a,** which was recrystallized twice in cyclohexane, giving colorless crystals mp 80–82°C; ^1H NMR ($CDCl_3$) δ, 1.97 and 2.28 (2s, 3H, CH_3S) Z-isomer 20% and E-isomer 80%, 5.72 (d, J = 14.7 Hz, H, =CH—CO), 6.10 (d, J = 11 Hz, H, =CH—C), 7.23 (dd, J = 11 Hz and J = 14.7 Hz, H, CH=CH—CH); mass spectrum m/e 306 (m^+). Anal. Calcd. for $C_{17}H_{22}O_3S$: C, 66.63; H, 7.24; S, 10.47. Found: C, 66.87; H, 7.25; S, 10.43.

*Ethyl 5-*p*-methoxyphenyl-2-methyl-5-methylthio-2,4-pentadienoate* **14b:** was prepared from **13b** as described for **14a** above, white crystals, mp 107–108°C (cyclohexane), ^1H NMR ($CDCl_3$) δ, 1.97 (s, 3H, CH_3S), 6.57 (d, J = 11 Hz, H, =CH), 7.90 (d, J = 11 Hz, H, =CH); mass spectrum m/e 292 (m^+). Anal. Calcd. for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; S, 10.97. Found: C, 65.71; H, 6.75; S, 10.85.

Tert-butyl 5,5-bis(methylthio)-4-phenyl-2,4-pentadienoate **16a:** colorless oil obtained from **15a** as described for **14a** above, ^1H NMR ($CDCl_3$) δ, 2.17 and 2.32 (2s, 6H, CH_3S), 5.20 (d, J = 14.6 Hz, H, =CH), 8.30 (d, J = 14.6 Hz, H, =CH); mass spectrum m/e 322 (m^+).

N,N-*Dimethyl-5,5-bis(methylthio)-4-phenyl-2,4-pentadienamide* **16c:** prepared from **15c** as described for **14a** above, beige crystals, mp 83–84°C (hexane), ^1H NMR ($CDCl_3$) δ, 2.13 and 2.33 (2s, 6H, CH_3S), 5.67 (d, J = 15.1 Hz, H, =CH), 8.27 (d, J = 15.1 Hz, H, =CH); mass spectrum m/e 293 (m^+). Anal. Calcd. for $C_{15}H_{19}NOS_2$: C, 61.39; H, 6.53; N, 4.77. Found: C, 61.29; H, 6.66; N, 4.86.

Compound **15b** treated in the same way as **14a** was unchanged.

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Methylation of 1,4-adduct **5** *prepared from* N^1,N^1*-dimethyl-*N^2*-thiobenzoylformamidine* **3** *and tert-butyl α-lithioacetate*

The 1,4-adduct **5** (4 mmol) was prepared as described in the general procedure. To the resulting solution, 2.28 g of methyl iodide (16 mmol in 5 ml of dry THF) was added at −70°C. After stirring for 17 h at room temperature, the reaction mixture was hydrolyzed and the crude product isolated as for compound **6.** The colorless oil thus obtained was then chromatographed on a column of silica gel. Elution with benzene gave 0.42 g (38%) of tert-butyl 3-[α-(methylthio)-benzylidenimino]-propenoate, **17a,** as white crystals mp 67–69°C (hexane); ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, SCH_3), 5.92 (d, J = 12.8 Hz, H, =CH), 7.73 (d, J = 12.8 Hz, H, =CH); mass spectrum m/e 277 (m^+). Anal. Calcd. for $C_{15}H_{19}NO_2S$; C, 64.95; H, 6.90; N, 5.05; S, 11.56. Found: C, 65.13; H, 6.91; N, 5.09; S, 11.35.

Methylation of 1,4-adduct **5** *prepared from* N^1,N^1*-dimethyl-*N^2*-thiobenzoylformamidine* **3** *and pinacolone lithium enolate*

This was carried out as described above for compound **17a.** The crude product was chromatographed on a column of silica gel. Elution with benzene gave 0.06 g (6%) of methyl *N*-(4,4-dimethyl-3-oxo-1-penten-1-yl)-thiobenzimidate **17b,** as pale yellow crystals mp 61–63°C (hexane): ^{1}H NMR ($CDCl_3$) 2.47 (s, 3H, SCH_3), 6.53 (d, J = 12.5 Hz, H, =CH—CO), 7.77 (d, J = 12.5 Hz, H, =CH—N); mass spectrum m/e 261 (m^+). Elution with a mixture of benzene-ether (10:1) gave an oil corresponding to the 1-dimethylamino-4,4-dimethyl-1-penten-3-one[20] (yield 40%).

*2-Ethoxycarbonyl-5-*p*-methoxyphenyl-2-methyl-3-pyrrolidino-2,3-dihydrothiophene* **18**

The ethyl α-chloropropionate lithium enolate was prepared as described in the general procedure from 1.36 g of 2-chloroethyl propionate (10 mmol) and 10.2 equivalents of LDA.

The 1-*p*-methoxyphenyl-3-pyrrolidino-2-propen-1-thione **1**(4 mmol) was added to the reaction mixture at −60°C. After complete discoloration, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The resulting reddish-orange solution was then hydrolyzed and after extraction with benzene the crude product was chromatographed on a column of silica gel. Elution with a mixture benzene-ether (4:1) gave 1.18 g (84%) of 2-ethoxycarbonyl-5-*p*-methoxyphenyl-2-methyl-3-pyrrolidino-2,3-dihydrothiophene **18,** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, J = 7 Hz, 3H, CH_3CH_2), 1.72 (s, 3H, CH_3), 1.75 (bs, 4H, CH_2 β to N), 2.78 (bs, 4H, CH_2 α to N), 3.73 (s, 3H, CH_3O), 4.20 (q, J = 7 Hz, 2H, CH_2CH_3), 4.69 (d, J = 2.5 Hz, H, CH—N), 5.88 (d, J = 2.5 Hz, H, CH=C), 7.10 (2d, J = 8.5 Hz, 4H aromatics); mass spectrum m/e 347 (m^+).

4-Dimethylamino-5-ethoxycarbonyl-5-methyl-2-phenyl-2-thiazoline, **19a**

This was prepared following the procedure described for compound **18** from the ethyl α-chloropropionate lithium enolate and N^1,N^1-dimethyl-N^2-thiobenzoylformamidine **3** (4 mmol).

The crude product was chromatographed on a column of silica gel. Elution with benzene gave 1.0 g (86%) of the 4-dimethylamino-5-ethoxy carbonyl-5-methyl-2-phenyl-2-thiazoline **19a** as a pale yellow oil; ^{1}H ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3H, CH_2CH_3), 1.72 (s, 3H, CH_3), 2.47 (s, 6H, $N(CH_3)_2$), 4.12 (q, J = 7 Hz, 2H, CH_2CH_3), 5.68 (s, H), 7.55 (m, 5H aromatics); mass spectrum m/e 292 (m^+).

4-Dimethylamino-5-ethoxycarbonyl-5-methyl-2-methylthio-2-thiazoline **19b** *and 3,6-diethoxycarbonyl-2-dimethylamino-3,6-dimethyl-4-thia-1-azabicyclo [3.1.0] hexane* **20**

These compounds were prepared following the procedure described for compound **18** using the ethyl α-chloropropionate lithium enolate and ethyl (dimethylaminoethylene)-dithiocarbamate, which had been previously prepared by the condensation of dimethylformamide diethyl acetal on methyl dithiocarbamate.[22]

The crude product was chromatographed on a column of silica gel. Elution with a mixture of benzene-ether (10:1) gave 0.32 g (25%) of the 4-dimethylamino-5-ethoxycarbonyl-5-methyl-2-methylthio-2-thiazoline **19b** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H, CH_3CH_2), 1.63 (s, 3H, CH_3), 2.36 (s, 3H, $N(CH_3)_2$), 2.51 (s, 3H, SCH_3), 4.10 (q, J = 7 Hz, 2H, CH_3CH_2), 5.41 (s, H); mass spectrum m/e 262 (m^+).

Elution with a mixture of benzene-ether (5:1) gave 0.47 g (22%) of the 3,6-diethoxycarbonyl-2-

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dimethylamino-3,6-dimethyl-4-thia-1-azabicyclo [3.1.0] hexane **20** as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (2t, J = 7 Hz, 6H, CH_3CH_2), 1.43 (s, 3H, CH_3), 2.42 (s, 6H, $N(CH_3)_2$), 2.48 (s, 3H, SCH_3), 4.00 (2q, J = 7 Hz, 4H, CH_3CH_2), 5.42 (s, H); mass spectrum m/e 362 (m^+).

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