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GENERATION AND CYCLOADDITIONS OF 2-(N-ACYLAMINO)-1-THIA-1,3-DIENES. PART II. RATIONALIZATION OF REACTIVITY USING AN FMO APPROACH.

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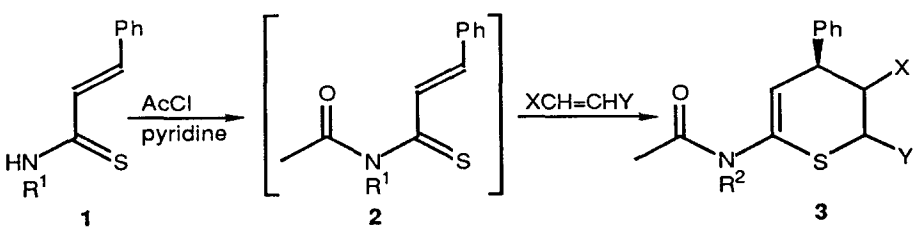
Abstract - 2-(N-Acylamino)-1-thia-1,3-dienes undergo regiospecific and stereoselective Diels-Alder cycloaddition to electron deficient, non-activated, and electron rich alkenes to give usefully functionalised dihydrothiopyrans in good yields.

Thiopyran rings are important structural features of a number of pharmacologically active systems.[2] In addition, thiopyrans are useful synthetic intermediates and can be transformed into a number of structurally important systems, notably cyclopentenes via Ramberg-Bäcklund type methodologies.[3] Clearly, an approach which leads to the rapid construction of these molecules and which allows a high level of control over the regio- and stereochemistry of any substituents present will be an extremely useful route to these heterocyclic systems.

In a preceding paper,[4] we reported that 2-(N-acylamino)-1-thia-1,3-dienes **2**, generated from acylation of α,β - unsaturated thioamides **1**, undergo regio- and stereospecific Diels-Alder cycloaddition to the starting thioamides **1** to yield usefully functionalised 3,4-dihydro-2H-thiopyrans **3** (X=CSNHR, Y=Ph) (Scheme 1).

We describe below the facile regiospecific and highly stereoselective cycloadditions of these reactive heterodienes **2** to a range of other dienophiles to produce the corresponding thiopyrans **3** in good yields. (Scheme 1).



SCHEME 1.

Results and discussion

Synthesis

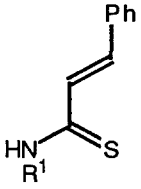
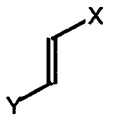
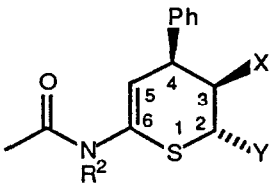
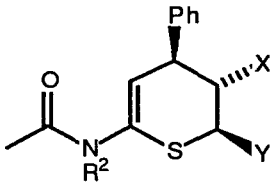
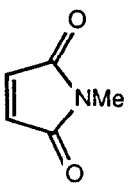
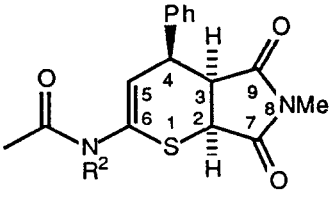
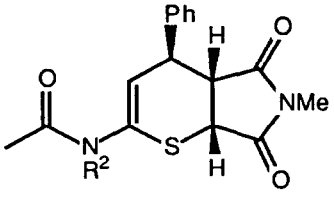
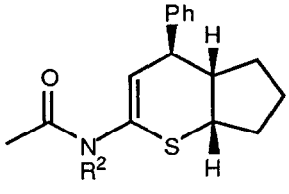
As a general procedure, two equivalents of acetyl chloride were added to a solution containing the thioamide precursor **1** and the dienophile (1.1 equivs.) in a pyridine/acetone mixture at 60°C, and this solution heated for a further 18 hrs. Product isolation then involved aqueous work-up followed by chromatography. The results of a number of experiments are summarised in Table 1.[5]

It was found that changing the temperature or the relative amounts of reactants did not increase the yield of thiopyrans. As noted previously,[4,6] use of thiocinnamamide **1** (R^1=H) as precursor gave substantial amounts of cinnamonitrile as by-product, which presumably results from competing S-acylation followed by elimination of thioacetic acid. Moreover, in the cycloadditions involving thiocinnamamide **1** (R^1=H) as precursor and dimethyl fumarate as dienophile, bis- and mono- N-acylated thiopyrans **4** (Table 1) are obtained. Bis-N-acylated species **9** and **11** are also obtained from other cycloadditions involving thiocinnamamide as precursor. The bis-acyl systems could arise via acylation with excess acid chloride of a first-formed thiopyran product **3** (R^2=H) resulting from cycloaddition of N-acylaminodiene **2** (R^1=H) with the dienophile. Alternatively, they could arise via *in situ* acylation of thiadiene **2** (R^1=H) to yield the N,N-bis-acylaminothiadiene **2** (R^1=COMe) followed by cycloaddition to the dienophile. For cycloadditions involving N-ethyl thiocinnamamide, the expected N-acyl, N-ethyl thiopyrans are obtained from cycloaddition of N-acyl thioamide **2** (R^1=Et) with the dienophile.

From inspection of the data in Table 1 it is clear that a wide range of dienophiles will participate in these cycloaddition reactions and that N-acyl thiocinnamamides undergo cycloaddition to electron rich (**7**), neutral (**10**, **11**) and electron deficient (**4**, **5**, **6**, **8** and **9**) dienophiles. In addition, all cycloadditions are stereoselective and, with the exception of reactions involving cyclopentene, favour formation of the *endo*-cycloadducts. Cycloadditions involving non-symmetrical dienophiles also display a striking regiospecifity, the observed regiochemistry depending on the nature of the dienophile.

It has been reported[7] that 3-aryl-2-cyanothioacrylamides exist in equilibrium with their [4 + 2] dimers at room temperature. However, in our case, the thioamides themselves were found to be completely unreactive towards dienophiles, and were recovered in full even after prolonged heating with a dienophilic trap. In addition, as reported previously,[4,6] NMR examination of a solution of thioamide **1** (R^1=H) in a mixture of pyridine and acetone at a range of different temperatures revealed only the presence of the thioamide and no dimers could be detected. As discussed in the following sections, these results are consistent with the generation of the N-acylaminothiadienes **2** as the reactive intermediates.

Table 1. [4+2] Cycloadditions of N-acyl thioamides (**2**).

Thioamide (1)	Dienophile	Products		Yield (%)[a]
				
R^1 = H	X = Y = CO_2Me	**4a** R^2 = COMe X = Y = CO_2Me	**4b** R^2 = COMe X = Y = CO_2Me	38[b](4:1)
		4c R^2 = H X = Y = CO_2Me	**4d** R^2 = H X = Y = CO_2Me	6 (4:1)
R^1 = Et	X = Y = CO_2Me	**5a** R^2 = Et X = Y = CO_2Me	**5b** R^2 = Et X = Y = CO_2Me	83 (4:1)
R^1 = Et	X = CN, Y = H	**6** R^2 = Et X = CN, Y = H		50
R^1 = Et	X = H, Y = OEt	**7a** R^2 = Et X = H, Y = OEt	**7b** R^2 = Et X = H, Y = OEt	30 (1:4)
				
R^1 = Et		**8a** R^2 = Et	**8b** R^2 = Et	60 (4:1)
R^1 = H		**9a** R^2 = COMe	**9b** R^2 = COMe	61[b](2:1)
				
R^1 = Et		**10** R^2 = Et		86
R^1 = H		**11** R^2 = COMe		47[b]

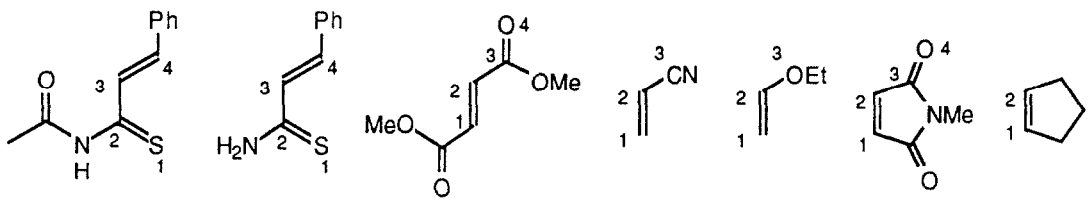
[a] The ratio of isomers is given in parentheses and has been determined from the NMR spectra of the isomeric mixtures. [b] In addition, a substantial amount of cinnamonitrile was isolated. For convenience in presenting the NMR data, the numbering of the bicyclic systems is given differently from the IUPAC numbering.

FMO examination of cycloaddition reactions

In order to attempt to rationalize the reactivity of the proposed N-acylaminothiadiene intermediates, and the observed regio- and stereoselectivity in their cycloaddition reactions, FMO calculations have been performed using FMO energies and orbital coefficients derived from CNDO/2[8] calculations. For the N-acyl thioamide intermediate **2** (R^1=H) (Scheme 1), four different fully-planar structures, differing in the conformation of the N-COMe moiety, can be envisaged. However, *ab-initio* MO calculations at the STO-3G level on each of these structures indicate that structure **A**[8] (below) is the lowest energy conformation and has thus been used for the following FMO analysis.

The calculated FMO energies and coefficients for compounds **A**-**G** are given in Tables 2 and 3, respectively.

In preceding papers[4,6] we report that in the absence of added dienophiles the N-acyl thioamides undergo cycloaddition with the starting thioamides or undergo dimerization to give thiopyrans **3** (eg. R^2=COMe, X=CSNHAc, Y=Ph) (Scheme 1). Inspection of the HOMO and LUMO energies in Table 2 indicates that those of N-acyl thioamide **A** are 0.46 eV closer in energy than the corresponding orbitals



A **B** **C** **D** **E** **F** **G**

Table 2. Frontier orbital energies (eV)[a]

Compound	E_{HOMO}	E_{LUMO}	ΔE
A	-9.932	0.000	9.93
B	-9.823	0.571	10.39
C	-13.306	0.732	14.04
D	-14.721	3.627	18.35
E	-12.134	5.575	18.71
F	-12.424	0.011	12.44
G	-12.841	4.417	17.26

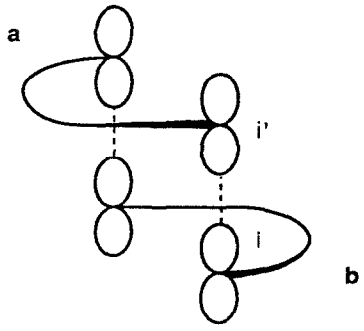
[a] Unmodified values from CNDO/2 calculations.

Table 3. Frontier orbital coefficients.

atom	1		2		3		4	
Comp.	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
A	-0.7821	0.4845	-0.2350	-0.4730	0.2309	-0.2063	0.3132	0.4980
B	-0.8381	0.4064	-0.2269	-0.4534	0.1819	-0.2736	0.2551	0.4951
C	0.3669	-0.4928	0.3669	0.4928	-0.1766	0.3011	-0.5271	-0.3811
D	-0.5919	-0.6569	-0.4963	0.5512	0.3537	0.2988	-	-
E	0.5876	-0.6651	0.3819	0.7197	-0.6443	-0.1732	-	-
F	0.0787	0.2836	-0.1299	-0.5239	-0.1299	0.5239	0.0787	-0.2836
G	0.5096	0.7524	0.5096	-0.7524	-	-	-	-

in thioamide **B**, thus promoting the dimerization of **A**. Alternatively, for the cycloaddition of N-acyl thioamides with starting thiocinnamamide **B**, the important FMO interaction clearly involves the HOMO of the diene and the LUMO of the dienophile (ΔE = 9.83 eV) which is 0.56 eV less than the corresponding orbital energy difference which would exist for the hypothetical dimerization of **B**, again accounting for the observed reactivity of N-acyl thioamides over that of the thiocinnamamide precursors. However, similar consideration of the energy differences for the important interactions for cycloaddition of **A** and **B** with each of the dienophiles **C**-**G**, respectively, predicts the opposite result as here, the energy gaps for cycloaddition of **B** are lower than those for **A**, in complete contrast to our experimental observations. However, as demonstrated in the following section, a more complete FMO analysis is required in order to reconcile experiment with theory.

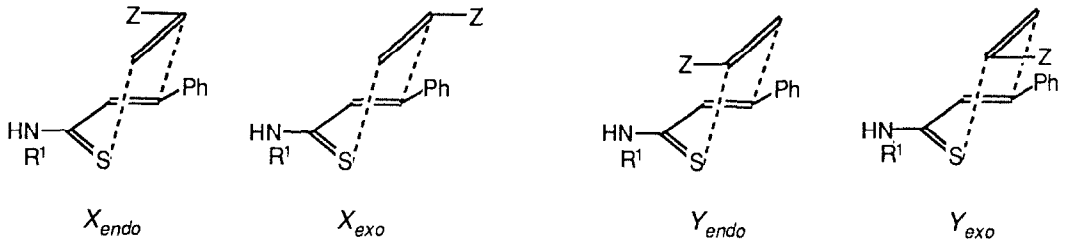
It has been noted by Ewing[7] that consideration of orbital energies alone can give misleading predictions concerning reactivity. Proper application of FMO theory requires consideration of the magnitude of the overlap between the participating orbitals as well as the orbital energies. Accordingly, interaction energies were calculated following the perturbational treatment of Salem.[9] For two reacting molecules **a** and **b**, the interaction energy E_{int} (neglecting the Coulombic term), is given by equation (1),[10] where c denotes the orbital coefficients of atomic centres i and i', E^H and E^L are the HOMO and LUMO energies in molecules **a** and **b**, respectively, and $\beta_{ii'}$ is the resonance overlap integral between atoms i and i'.



$$E_{int} = -2\left(\sum_{i\,i'} c^{H}_{ib} c^{L}_{i'a} \beta_{ii'}\right)^2 / \left(E^{L}_{b} - E^{H}_{a}\right) - 2\left(\sum_{i\,i'} c^{L}_{ib} c^{H}_{i'a} \beta_{ii'}\right)^2 / \left(E^{L}_{a} - E^{H}_{b}\right) \quad (1)$$

In order to simplify the task of solving equation (1) for the present cycloadditions, a number of assumptions have been made: *a)* the resonance overlap integrals for C-C and C-S bond formation, β_{CC} and β_{CS}, respectively, have the same magnitudes; a value of 5.0 eV corresponding to a separation of 2.0 Å between reacting centres[11] has been used; for C-O bond formation, a value of 3.77 eV for β_{CO} has been used; *b)* for an *"endo"* addition (see below), the resonance overlap integrals for the primary orbital interaction are equal to those involved in the secondary orbital interaction.

For transition states for cycloadditions to non-symmetrical dienophiles, two regioisomeric orientations, *X* and *Y* are possible (Fig. 1). In addition, there is the possibility for two stereoisomeric arrangements within each of these (denoted using the subscripts *endo* and *exo* - Fig. 1).



X_{endo} X_{exo} Y_{endo} Y_{exo}

Figure 1

Moreover, *endo* transition states involving a dienophile which is able to adopt a *cisoid* relationship with an unsaturated conjugating substituent (structures **A**, **B** and **C**) are considered to involve four points of interaction.[12] Thus, representative structures for the transition states for the dimerization of **A** and for the cycloaddition of **A** with **B** and with **C** are given in Fig. 2. The calculated interaction energies are given in Table 4.

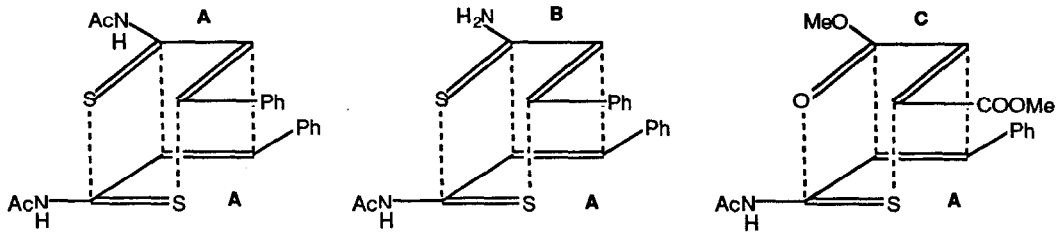


Figure 2

Table 4. Calculated interaction energies $-E_{int}$ (eV) for transition states *X* and *Y*.

dienophile	A[a]				B[a]				C[b]	
diene	X_{endo}	X_{exo}	Y_{endo}	Y_{exo}	X_{endo}	X_{exo}	Y_{endo}	Y_{exo}	*endo*	*exo*
A	4.67	1.40	2.94	0.87	4.36	1.30	2.89	0.88	3.87	3.18
B[f]	4.05	-	-	-	4.05	-	-	-	3.58	-

dienophile	D[c]				E[d]				F[e]	
diene	X_{endo}	X_{exo}	Y_{endo}	Y_{exo}	X_{endo}	X_{exo}	Y_{endo}	Y_{exo}	*endo*	*exo*
A	3.35[g]	2.71	3.52[h]	2.47	2.94	2.65	3.67	2.79	2.63	1.72
B[i]	3.18	-	-	-	-	-	2.91	-	2.52	-

dienophile	G
diene	-
A	3.34
B[i]	3.16

[a] *Endo* and *exo* are used to refer to the relative orientations of the thiocarbonyl moiety. [b] *Endo* and *exo* have been arbitrarily chosen to refer to the relative orientation of the carbonyl group on the carbon atom involved in bonding to C-4 of **A** and **B**, respectively. [c] The *endo* transition states involve a secondary orbital interaction of the nitrile carbon (C-3 in **D**). [d] The *endo* transition states involve a secondary orbital interaction of the oxygen atom. [e] The *endo* transition states involve two secondary orbital interactions of the carbonyl carbons. [f] Only interaction energies involving an X_{endo} transition state have been calculated. [g] Consideration of an additional secondary orbital interaction involving the nitrile N and carbonyl O increases $-E_{int}$ for this configuration to 3.48 eV. [h] Consideration of an additional secondary orbital interaction involving the nitrile and amide N's reduces $-E_{int}$ for this configuration to 2.66 eV. [i] With the exception of cycloadditions to **E**, only interaction energies involving an X_{endo} transition state have been calculated.

A number of points emerge from consideration of the data in Table 4. In contrast to the anomalous predictions concerning the relative reactivity of **A** and **B** to dienophiles from FMO energies alone, comparison of the corresponding interaction energies now reinforces experimental observations. In all

cases, the interaction energies of **A** are greater than the corresponding values for **B**, thus predicting a greater reactivity for intermediate **A**.

For cycloadditions involving non-symmetrical dienophiles, comparison of the predicted interaction energies for the *X* and *Y* regioisomeric configurations for a particular cycloaddition confirms the regiospecificity observed in practice; eg. in the cases of the dimerization of **A**, and its cycloaddition to **B**, the values for the *X* configuration are always greater than the corresponding values for the *Y* addition mode. In this connection, it is interesting to note that in the case of cycloaddition of **A** to vinyl ether **E**, it is the Y_{endo} configuration (leading to formation of thiopyran **7b**, Table 1) that is predicted to be more energetically favourable, in complete accord with experimental observation. In addition, for dienophiles substituted with conjugating, electron withdrawing substituents, it can be seen that the *endo* transition state (for explanations of the exact meaning of this term for a particular cycloaddition, see Fig. 1 and the notes in Table 4) is always favoured, in accord with the observed preference for formation of thiopyrans derived from *endo* addition of diene and dienophile (Table 1). An interesting exception to the predominance of the X_{endo} configuration for non-symmetrical electron deficient dienophiles is the case of cycloaddition of **A** to acrylonitrile **D**, where the Y_{endo} interaction energy is the greater, thus predicting formation of the regioisomer to thiopyran **6** (Table 1). This contrasts sharply with the regio- and stereospecific formation of **6** (Table 1) observed in practice. However, inspection of molecular models for the X_{endo} transition state for this cycloaddition reveals the possibility of a second secondary orbital interaction involving the nitrogen atom of the nitrile and the oxygen atom of the N-acyl moiety (Fig. 3.)

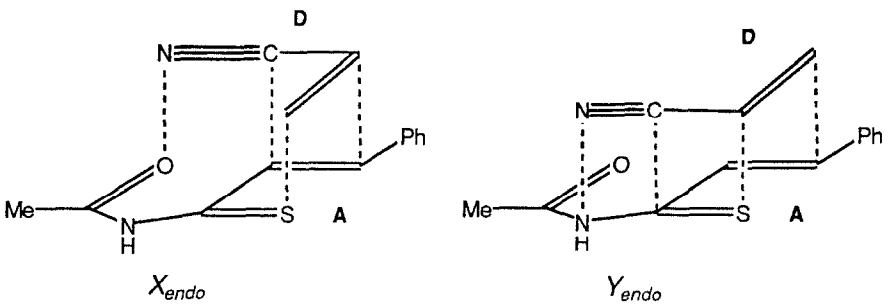


Figure 3

In particular, the model indicates that at a distance of 2.0 Å between the primary reacting centres for **A** and **D**, respectively, the nitrile nitrogen and the oxygen atoms are 2.5 Å apart. Thus, using a value of 1.04 eV for β_{NO} as calculated by Houk,[11] the interaction energy is now -3.48 eV. In addition, similar consideration of the Y_{endo} transition state configuration indicates that the nitrogens of the nitrile and amide moieties are 2.0 Å apart and will have an antibonding $LUMO_{diene}$- $HOMO_{dienophile}$ interaction.

Using β_{NN} as 3.65 at 2.0 Å ,[11] the interaction energy is reduced to -2.66 eV, thus accounting for the observed preference of the X_{endo} configuration.

Clearly, in a number of cases, additional factors can operate which have been ignored in the above analysis. For instance, for the dimerizations of **A** and of **B** and for the cycloaddition of **A** with **B**, the Y_{endo} configuration can also involve a second secondary orbital bonding interaction between the nitrogens of the two interacting species. However, this configuration also involves a considerable steric repulsion between the phenyl groups, which should oppose this secondary bonding interaction and thus favour the observed X_{endo} cycloaddition mode. Nevertheless, the general trends which result from the above FMO treatment are in good agreement with experimental observations.

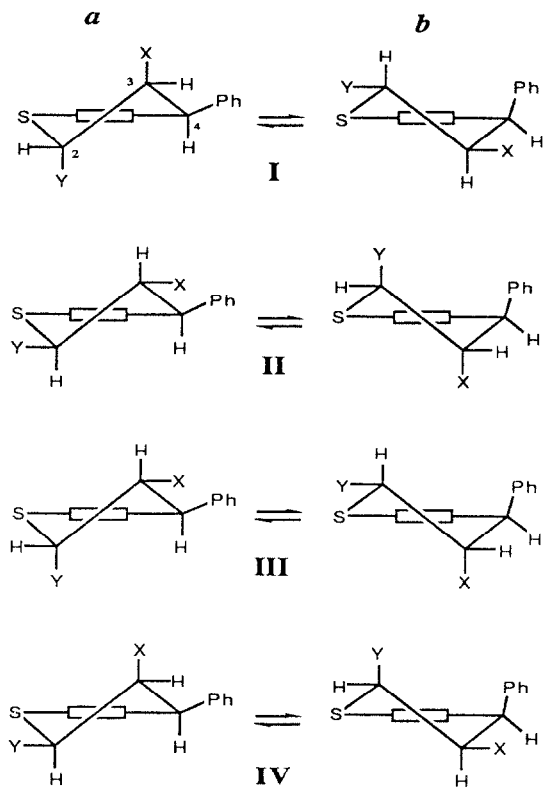
In order for valid comparisons to be made between theoretical and actual stereo- and regiochemistry in the cycloaddition products, it was necessary to rigorously establish the stereochemical details for all the thiopyran products as detailed below.

Structure Determinations

The constitutions, relative configurations and major conformations of compounds **4-11** were established by NMR studies employing the concerted use of one-dimensional (1D) $^1H\{^1H\}$ NOE difference experiments together with ^1H-^1H (COSY) and ^{13}C-^1H (HETCOR) shift correlated 2D methods. For each compound a preliminary ^1H and ^{13}C assignment was straightforward, and was supported in a number of cases[13] by COSY and HETCOR experiments. (^1H chemical shifts are given in the experimental section; the structurally important vicinal J(H,H) couplings are collected in Table 5, characteristic ^{13}C chemical shifts are listed in Table 8).

The stereostructures were then investigated mainly by $^1H\{^1H\}$ NOE measurements using a similar approach to that discussed previously.[4] (Results of the homonuclear NOE experiments, together with a list of the stereochemically diagnostic through-space connectivities reflected by them are collected in Table 6). No assumptions about stereochemistry based on the likely outcome of the relevant Diels-Alder reactions were made (especially since, according to our earlier observations,[4] epimerization might potentially invalidate such premises), and stereochemical assignment is based entirely on spectroscopic grounds. Accordingly, for compounds **4-7** the corresponding four possible diastereoisomers with the two main half-chair conformations of the thiopyran ring were considered (Scheme 2). Similarly, the 3D representation of the two conceivable diastereoisomers and the two boat conformations of the six-membered ring for compounds **8-11** is illustrated in Scheme 3. (For the latter the *cis* relationship of H-2 and H-3 is chemically unambiguous, and is also readily reflected by their short interproton distance manifested in the NOE results - Table 6). In an analogous manner to our previous considerations,[4] each individual stereostructure in Schemes 2 and 3 can be characterized by a unique combination of "short" and "long", structurally diagnostic d(i;j) H-H interproton distances (herein "short"

refers to a spatial H-H arrangement which should, according to model-considerations, allow the development of readily detectable steady-state NOEs, while "long" corresponds to a distance through which no appreciable first-order enhancements are expected to be observed). In order to aid interpretation of the NOE results in relation to the appropriate stereochemical possibilities, these distance-combinations are listed in Table 7. A comparison of the observed NOE connectivities (Table 6) with Table 7, used, where appropriate, in conjunction with the $^3J(H,H)$ couplings collected in Table 5, readily defines the relative configuration and the preferred conformation of the thiopyran ring for each Diels-Alder adduct. In some cases the NOE measurements also resolved remaining ambiguities in the ^1H assignments, notably concerning the methylene ring-protons in **6** and **7** (*vide infra*), and also by locating the C4-Ph *ortho* protons (usually hidden among the non-first-order aromatic ^1H signals at 400 MHz) upon the irradiation of H-4. (Thus identifying the *ortho* protons by quick preliminary NOE measurements allowed them to be included in the NOE irradiation sequence for some compounds).



SCHEME 2

Table 5. Characteristic ^3J(H,H) vicinal coupling constants (Hz) for compounds **4-11.**

H,H	4a	4b	4c	4d	5a	5b
2,3	11.4	9.9	11.6	9.8	11.0	9.6
3,4	4.7	9.9	5.0	9.8	5.0	9.6
4,5	6.5	3.0	6.5	3.0	6.4	3.1

H,H	7a	7b	H,H	6
2,3β	2.0	8.6	**2β,3**	7.0
2,3α	4.3	3.0	**2α,3**	2.7
3β,4	12.6	8.6	**3,4**	5.0
3α,4	4.3	6.0	**4,5**	3.8
4,5	2.5	3.1		

H,H	8a	8b	9a	9b	10	11
2,3	9.0	9.0	9.2	9.0	*a*	*a*
3,4	*a*	3.7	4.0	3.9	5.3	5.3
4,5	5.3	7.4	5.3	7.8	5.3	5.3

a Coupling not clearly resolved, or hidden by overlaps.

Table 8. Selected ^{13}C chemical shifts δ(ppm) ($CDCl_3$) for compounds **4-11.**

carbon No.:	4a	4b	5a	5b	6	7a	7b
C-2	40.4	46.4	40.4	45.9	41.6	80.6	82.2
C-3	45.5	48.9	45.3	48.8	31.5	37.4	38.8
C-4	42.5	45.5	42.2	44.9	42.6	37.7	40.8
C-5	126.0	127.5	123.4	125.4	122.4	126.4	126.4
C-6	131.8	130.9	135.0	134.3	138.2	133.2	135.0
other					117.6 (CN)		

	8a	8b	9a	9b	10	11
C-2	45.1	42.5	45.3	43.1	43.0	44.1
C-3	50.0	47.0	50.2	48.0	45.9	47.3
C-4	45.1	40.8	45.6	41.2	44.5	45.6
C-5	130.0	127.9	134.5	132.5	123.5	126.7
C-6	137.2	136.6	134.5	134.7	136.2	133.7

Table 6. Results of the 1D $^1H\{^1H\}$ NOE difference experiments on compounds **4-11**. [The measured NOE intensities are arbitrarily denoted as "s" (strong, >8%), "m" (medium, 3-8%) and "w" (weak, ≈1-3%)].

compound	irradiated proton	observed enhancement							*stereostructurally diagnostic short distances:*
		H-2	**H-3**	**H-4**	**H-5**	**o-4**[a]			
	H-2	*	-	-	-	s			
	H-3	-	*	s	-	-			d(2;o-4); d(3;4)
4a,5a	H-4	-	s	*	s	s			
	o-4	m	-	m	w	*			
	H-2	*	m	m	-	-			d(2;3); d(2;4);
	H-3	m	*	w	-	m			d(3;4); d(3;o-4);
4b,5b	H-4	s	w	*	m	s			
	o-4	-	m	w	w	*			
		H_β-2	**H_α-2**	**H-3**	**H-4**	**H-5**	**o-4**		
	H_β-2	*	*b*	m	-	-	-		
	H_α-2	*b*	*	*b*	m	-	-		d(2β;3); d(2α;4);
6	H-3	w	*b*	*	s	-	w		d(3;4)
	H-4	-	w	s	*	m	s		
	o-4	-	-	w	m	w	*		
		H-2	**H_β-3**	**H_α-3**	**H-4**	**H-5**	**o-4**	**other**	
	H-2	*	m	m	-	-	-	OCH_xH_yMe(m)	d(2;3β); d(2;3α);
7a	H_β-3	m	*	s	-	-	w		d(4;3α)
	H_α-3	m	s	*	m	-	-		
	H-4	-	-	w	*	w	m		
	H-2	*	-	m	m	-	-	OCH_xH_yMe(m)	d(2;3α); d(2;4);
7b	H_β-3	w	*	s	w	-	w		d(2;3β); d(4;3β)
	H_α-3	m	s	*	m	-	-		d(4;3α)
	H-4	m	-	m	*	m	m		
	H-2	*	s	m	-	-			d(2;3); d(2;4);
	H-3	s	*	m	-	s			d(3;4); d(3;o-4)
9a	H-4	w	m	*	w	s			
	o-4	-	w	m	s	*			
	H-2	*	s	-	-	w			d(2;3); d(2;o-4);
	H-3	s	*	m	-	m			d(3;4); d(3;o-4)
9b	H-4	-	m	*	s	s			
	o-4	w	w	w	w	*			
		H-2	**H-3**	**H-4**	**H-5**	**o-4**	**other**		
	H-2	*	s	-	-	m	H_β-7(m)[c]		d(2;3); d(2;o-4);
10,11	H-3	m	*	m	-	m	H_β-9(m)[c]		d(3;4); d(3;o-4)
	H-4	-	m	*	s	s	H_α-9(m)[c]		
	o-4	w	m	m	w	*	-		

[a] o-4 refers to the C2-Ph and C4-Ph *ortho* protons, respectively. [b] The observed signal is affected by some "spill-over" from the irradiation of the adjacent target signal, which leads to an unclear result. [c] Signal attributed to the α or β site in view of the stereostructure deduced from independent NOE results.

Table 7. Unique combinations of "short" (S) and "long" (L) d(i;j) H-i--H-j interproton distances for the stereostructures shown in Schemes 2 and 3. "S" refers to a spatial H-H arrangement which should allow the development of readily detectable NOEs, while "L" corresponds to a distance through which practically no first-order enhancements are expected to be seen.

Compounds **4-5**

	Ia	**Ib**	**IIa**	**IIb**	**IIIa**	**IIIb**	**IVa**	**IVb**
d(2;o-4)[a]	L	**S**	L	L	L	**S**	L	L
d(2;3)	**S**	L	L	**S**	**S**	**S**	**S**	**S**
d(2;4)	L	L	**S**	L	L	L	**S**	L
d(3;o-4)	**S**	L	**S**	**S**	**S**	**S**	**S**	L
d(3;4)	**S**	**S**	L	**S**	L	**S**	**S**	**S**

Compounds **7a,7b** (X=H)

	Ia	**Ib**	**IIa**	**IIb**
d(2;o-4)	L	**S**	L	L
d(2;3β,α)	**S,S**	**S,L**	**L,S**	**S,S**
d(2;4)	L	L	**S**	L
d(4;3β,α)	**L,S**	**S,S**	**L,S**	**S,S**

Compound **6** (Y=H)

	Ia	**Ib**	**IIa**	**IIb**
d(2β;o-4)	L	**S**	L	**S**
d(2α;4)	**S**	L	**S**	L
d(3;2β,α)	**S,S**	**L,S**	**S,L**	**S,S**
d(3;4)	**S**	**S**	L	**S**

Compounds **8-11**

	Aa	**Ab**	**Ba**	**Bb**
d(2;o-4)	**S**	L	L	L
d(2;3)	**S**	**S**	**S**	**S**
d(2;4)	L	L	*d*	**S**
d(3;o-4)	**S**	**S**	L	**S**
d(3;4)	**S**	L	**S**	**S**
d(o-4;9[c])[b]	L	L	**S**	**S**

[a] o-4 denotes the C-4--Ph *ortho* protons. [b] For **10** and **11** only. [c] 9α and/or 9β protons. [d] Categorization of this distance into "S" or "L" is not unambiguous.

More specific details of the stuctural investigations will be briefly discussed below.

For compounds **6**, **7a** and **7b** a distinction between the two possible regioisomers associated with the corresponding Diels -Alder reactions is readily resolved by tracing the proton coupling network in the thiopyran ring.

In compound **7a** the 12.6 Hz coupling between H-4 and one of the H-3 signals at δ 2.00 indicates a diaxial relationship between these protons. (The lack of NOE enhancement between them shows that their large coupling cannot be attributed to a nearly eclipsed arrangement - a possibility which for Hα-3 and H-4 in the "**b**" conformation cannot otherwise be confidently ruled out). This, in view of the possible stereostructures in Scheme 2, associates the geometry with the "**b**" conformation and identifies the

δ 2.00 ppm H-3 signal as being from the β hydrogen. Also, H-2 shows small couplings to both H-3 protons (*synclinal* arrangements). All this is consistent with a predominant "**Ia**" (="**IIIa**") structure only. The NOE results independently prove both this geometry and the assignment of the H-3 signals to the α and β sites (Tables 6 and 7). Note that in **7a** the "**Ia**" conformation, in which the OEt group occupies an axial position, compares favourably with "**b**", presumably because in "**a**" the repulsion among the O and S lone electron pairs is relieved.

For compound **7b** the short d(2;4) distance reflected by the NOE results identifies "**IIa**" (= "**IVa**") as a preferred conformation. Also, when irradiating H-2 or H-4, the weak and strong enhancements seen on the H_β-3 (δ 2.24) and H_α-3 (δ 2.49) signals, respectively, readily confirm their assignments to the β and α sites. The weak H-2--H_β-3 and H_β-3--H_α-4 NOE connections both indicate some contribution of "**IIb**" (="**IVb**") in the conformational equilibrium. This also accords with the relatively small $^3J(2\alpha,3\beta)$ and $^3J(3\beta,4\alpha)$ diaxial couplings (8.6 Hz). Again, the presence of "**IIb**" in the equilibrium may be attributed to the above mentioned O<-->S repulsion.

Note that for both **7a** and **7b**, the preliminary assignment of the H-3 signals to the α and β sites is not necessary in order to define the stereostructures by a comparison of Tables 6 and 7. Nevertheless, these assignments are also readily provided by the observed NOEs in a self-explanatory manner. (The only exception to this is the hypothetical situation of a predominant "**IIb**" structure where strong NOEs would be expected on both H_α-3 and H_β-3 by irradiating either H-2 or H-4). Interestingly, for both compounds, irradiation of H-2 produces an enhancement only on one of the diastereotopic OEt methylene protons. This indicates that the OEt group occupies a preferential conformation in which the average d(2;OCH_x) and d(2;OCH_y) distances are very different.

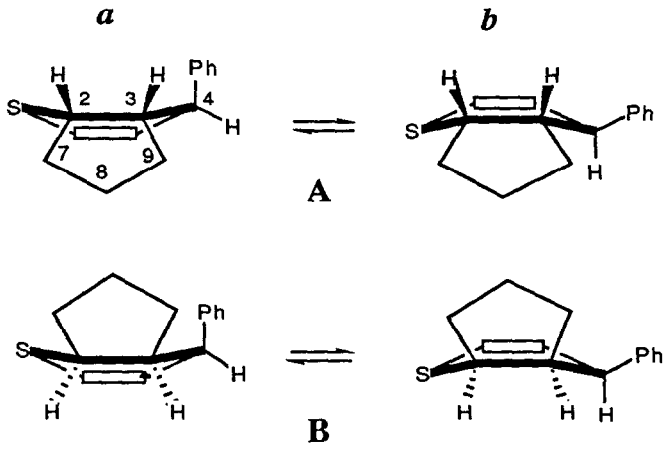
Some ^{13}C chemical shift differences between **7a** and **7b** are also characteristic. In **7a**, notably, δ C-4 is shifted 3.1 ppm upfield relative to its value in **7b** due to the *γ-gauche* steric effect of the OEt group.

In the case of **6**, the vicinal couplings (Table 5) are consistent with either a "**Ia**" (="**IVa**") or "**IIb**" (="**IIIb**") geometry. The NOE measurements, however, give conclusive evidence for "**Ia**". In this respect, the detected small d(2α;4) distance is notable, since this also allows a distinction between the H_α-2 and H_β-2 signals.

For compounds **4a** and **5a**, both the vicinal couplings and the NOE results clearly point to a predominant "**Ib**" stereostructure.

For **4b** and **5b**, on the other hand, the NOE connectivities are consistent either with a predominant "**IVa**" structure, or a "**IIa**"⇌"**IIb**" equilibrium. "**IVa**", However, is ruled out by

considering the relatively large $^3J(2,3)$ and $^3J(3,4)$ values, which are indicative of "**IIa**" as a preferential conformation. The fact that the $^3J(3,4)$ values are somewhat smaller than those found in **4b** and **5b** also reflects the presence of "**IIb**" in the equilibrium. For **4a** and **5a**, the C-2, C-3 and C-4 signals are all shifted upfield of their values in **4b** and **5b**, in accordance with the more axially oriented position of the Ph group in "**Ib**" relative to "**IIa**".



SCHEME 3

In the cases of **9b**, **10** and **11** the NOE information readily identifies the stereostructures as "**Aa**" (Scheme 3). For each of these compounds, any significant population of the "**Ab**" conformation can be ruled out on the basis of the small $^3J(3,4)$ couplings. The reason for a pseudo-axial Ph group being preferred is presumably to avoid the Ph<-->H_2-9 (in **10** and **11**) or Ph<-->C-9=O (**9b**) repulsions. For **9a** the geometry is assigned to "**Bb**", notably as reflected by the short d(2;4) and d(3;o-4) distances. In this case it is difficult to assess any possible contribution of "**Ba**" in the equilibrium from the measured NOEs or the $^3J(3,4)$ coupling. However, it is obvious that "**Ba**" involves a severe Ph<-->C-4=O steric interaction which makes its presence in any appreciable amounts unlikely. In **9b** the upfield shifts of the C-2, C-3 and C-4 signals relative to **9a** are again attributed to the Ph group becoming pseudo-axial in **9b**.

For **8a** ("**Bb**") and **8b** ("**Aa**") the stereostructures can be safely established by analogy with the respective ^1H and ^{13}C chemical shifts of **9a** and **9b**. (Owing to the presence of the NCH_2CH_3 protons in the mixture of the two isomers, the resulting overlaps precluded any meaningful NOE analysis in this system).

Experimental

Spectroscopy

All NMR spectra of compounds **4-11** were recorded on a Bruker AM-400 spectrometer operating at 400.13 and 100.61 MHz for ^{1}H and ^{13}C nuclei, respectively, with internal deuterium lock in $CDCl_3$ at ambient temperature (297K). Chemical shifts are given relative to δ_{TMS}=0.00 ppm. Two-dimensional (COSY and C-H correlated) and homonuclear NOE experiments were recorded by using the standard spectrometer software package. All NOEs were measured in non-degassed samples, using 4 s pre-irradiation times; FIDs were exponentially multiplied prior to Fourier transformation (LB = 1 - 3 Hz). ^{13}C multiplicities were determined by the APT method.[14]

Infra red spectra were recorded on a Perkin-Elmer 1420 ratio spectrometer and mass spectra on a Kratos-D5 spectrometer at 70eV E.I. Microanalyses were determined at the University of Leeds School of Chemistry microanalytical unit and melting points (uncorrected) on a Kofler hot stage apparatus.

Synthesis

N-Ethylthiocinnamamide (1, R^1=Et) and thiocinnamamide (1, R^1=H). For preparation and physical characterization see ref. 4.

Compounds 5a and 5b. A solution of acetyl chloride (1.5ml; 21.0mmol) in acetone (20ml) was added dropwise to a solution of N-ethylthiocinnamamide (2.0g;10.5mmol), dimethyl fumarate (1.7g; 11.5mmol) and pyridine (1.7ml; 21.0mmol) in acetone (20ml) at reflux. The resulting dark red solution was heated at 60°C at reflux for 18hr., during which time precipitation of pyridinium hydrochloride was observed. The reaction mixture was allowed to cool to room temperature and, after aqueous work-up and chromatography (SiO_2; 50% ethyl acetate/hexane), yielded 3.28g (83%) of an isomeric mixture of cycloadducts as a pale yellow solid. The cycloadducts were separated by fractional crystallisation from ether to give **5a** (2.56g; 71%, mp 108.5-110°C) and **5b** (0.36g; 10%).

5a ^{1}H NMR ($CDCl_3$), δ: 1.10 (3H, t, $-CH_2C\underline{H}_3$); 2.15 (3H, s, $COCH_3$); 3.31 (1H, dd, H-3); 3.48 (3H, s, OCH_3); 3.43-3.65 (2H, m, $-C\underline{H}_2CH_3$); 3.65 (3H, s, OCH_3); 4.12 (1H, dd, H-4); 4.23 (1H, d, H-2); 5.91 (1H, d, H-5); 7.04 (2H, dm, C4-Ph *ortho* protons). [For all compounds **4-11** the aromatic ^{1}H signals give non-first-order subspectra at 400 MHz (ca. 7.0 - 7.5 ppm in general). Here the *ortho* proton chemical shifts are given only, since these are easily identified in the ^{1}H NOE difference experiments, and are of special interest as regards the structural conclusions based on the NOE results].

5b ^{1}H NMR ($CDCl_3$), δ: 1.10 (3H, t, $-CH_2C\underline{H}_3$); 2.14 (3H, s, $COCH_3$); 3.16 (1H, t, H-3); 3.39 (3H, s, OCH_3); 3.43-3.65 (2H, m, $-C\underline{H}_2CH_3$); 3.53 (3H, s, OCH_3); 3.85(1H, dd, H-4); 4.44 (1H, d, H-2); 5.74(1H, d, H-5); 7.06 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3100-3000 (C-H) aromatic str., 3060 (=C-H) vinylic str., 3000-2800 (C-H) aliphatic str., 1735 (C=O) str., 1650 (C=O) str., 1600 (C=C) str. Analysis: calculated for $C_{19}H_{23}NO_5S$: C, 60.46%, H, 6.14%, N, 3.71%; found: C, 60.84%, H, 6.14%, N, 3.97%.
Ms (m/e). 377[M]$^+$, 190, 147, 113, 85, 69, 59, 43.
Accurate mass: calculated for $C_{19}H_{23}NO_5S$ 377.1296; found: 377.1303.

Compounds 4a and 4b. Prepared as above. A solution of thiocinnamamide (1.87g; 11.5mmol), dimethyl fumarate (1.82g; 12.6mmol) and pyridine (1.85ml; 23.0mmol) in acetone (15ml) was treated with a solution of acetyl chloride (1.63ml; 23.0mmol) in acetone (15ml). Aqueous work-up, then chromatography (SiO_2; 30% ethyl acetate/hexane), gave **4a-b** (1.7g; 38%, mp 157-159°C) and **4c-d** (0.245g; 6%, mp 70-72°C), both as isomeric mixtures of white solids.
4a ^{1}H NMR ($CDCl_3$), δ: 2.45 (6H, s, $N(COCH_3)_2$); 3.37 (1H, dd, H-3); 3.53 (3H, s, OCH_3); 3.66 (3H, s, OCH_3); 4.17 (1H, dd, H-4); 4.28 (1H, d, H-2); 5.98 (1H, d, H-5); 7.23 (2H, dm, C4-Ph *ortho* protons).
4b ^{1}H NMR ($CDCl_3$), δ: 2.44 (6H, s, $N(COCH_3)_2$); 3.23 (1H, t, H-3); 3.43 (3H, s, OCH_3); 3.60 (3H, s, OCH_3); 3.92 (1H, dd, H-4); 4.54 (1H, d, H-2); 5.84 (1H, d, H-5); 7.15 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3060 (=C-H) vinylic str., 3050-3000 (C-H) aromatic str., 3000-2800 (C-H) aliphatic str., 1950-1800 (overtone), 1750, 1720 (C=O)str., 1700 (C=O) str., 1595 (C=C) aromatic str. Analysis: calculated for $C_{19}H_{21}NO_6S$: C, 58.3%, H, 5.41%, N, 3.58%, S, 8.19%; found: C, 58.45%, H, 5.45%, N, 3.5%, S, 8.05%.
Ms (m/e). 391[M]+, 348, 230, 204, 162, 130, 113, 77, 59, 43.
Accurate mass: calculated for $C_{19}H_{21}NO_6S$ 391.1089; found: 391.1076

4c ^{1}H NMR ($CDCl_3$), δ: 2.04 (3H, s, $NCOCH_3$); 3.40 (1H, dd, H-3); 3.53 (3H, s, OCH_3); 3.67 (3H, s, OCH_3); 4.13 (1H, dd, H-4); 4.18 (1H, d, H-2); 6.00 (1H, d, H-5); 8.97 (1H, s, NH).
4d ^{1}H NMR ($CDCl_3$), δ: 2.02 (3H, s, $NCOCH_3$); 3.10 (1H, t, H-3); 3.41 (3H, s, OCH_3); 3.53 (3H, s, OCH_3); 3.80 (1H, dd, H-4); 4.40 (1H, d, H-2); 5.78 (1H, d, H-5); 9.07 (1H, s, NH).
IR (cm^{-1}): 3400 (N-H) str., 1720 (C=O)str., 1595 (C=C) aromatic str. Analysis: calculated for $C_{17}H_{19}NO_5S$: C, 58.21%, H, 5.48%, N, 4.01%; found: C, 58.05%, H, 5.35%, N, 4.06%.
Ms (m/e). 349[M]+, 306, 291, 290, 234, 115, 43.
Accurate mass: calculated for $C_{17}H_{19}NO_5S$ 349.0982; found: 349.0996

Compound 6. Prepared as above. A solution of N-ethylthiocinnamamide (500mg; 2.62mmol), acrylonitrile (0.19ml; 2.88mmol) and pyridine (0.43ml; 5.24mmol) in acetone (10ml) was treated with a solution of acetyl chloride (0.37ml; 5.24mmol) in acetone (10ml). Aqueous work-up, then chromatography (SiO_2; 50% ethyl acetate/hexane), gave **6** as a white solid (376mg; 50.2%, mp 107-109°C).

^{1}H NMR ($CDCl_3$), δ: 1.19 (3H, t, $NCH_2C\underline{H}_3$); 2.27 (3H, s, $COCH_3$); 3.23 (1H, dd, Hβ-2); 3.33 (1H, dd, Hα-2); 3.41 (1H, ddd, H-3); 3.55 (1H, br, $NC\underline{H}_xH_yCH_3$); 3.65 (1H, br, $NCH_x\underline{H}_yCH_3$); 3.95 (1H, dd, H-4); 5.82 (1H, d, H-5); 7.27 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 2235 (CN) str., 1650 (C=O) str.
Ms (m/e). 286[M]+, 233, 147,130, 115, 93, 80, 70, 61, 43.
Accurate mass: calculated for $C_{16}H_{18}N_2OS$ 286.1140; found: 286.1152

Compounds 7a and 7b. Prepared as above. A solution of N-ethylthiocinnamamide (1.68g; 8.8mmol), ethyl vinyl ether (0.92ml; 9.7mmol) and pyridine (1.42ml; 17.6mmol) in acetone (20ml) was treated with a solution of acetyl chloride (1.25ml; 17.6mmol) in acetone (20ml). Aqueous work-up, then chromatography (SiO_2; 30% ethyl acetate/hexane) gave **7b** (0.725g; 27%, mp 69-72°C) and **7a** (80mg; 3%, oil).
7a ^{1}H NMR ($CDCl_3$), δ: 1.15 (3H, t, $NCH_2C\underline{H}_3$); 1.25 (3H, t, $OCH_2C\underline{H}_3$); 2.00 (1H, ddd, Hβ-3); 2.18 (3H, s, $NCOCH_3$); 2.38 (1H, dt, Hα-3); 3.51 (1H, m, $OC\underline{H}_xH_yCH_3$); 3.57 (2H, broad, $NC\underline{H}_2CH_3$); 3.87 (1H, ddd, C4-H); 3.97 (1H, m, $OCH_x\underline{H}_yCH_3$); 5.01 (1H, dd, H-2); 5.78 (1H, d, H-5); 7.22 (2H, dm, C4-Ph *ortho* protons).
7b ^{1}H NMR ($CDCl_3$), δ: 1.15 (3H, t, $NCH_2C\underline{H}_3$); 1.15 (3H, t, $OCH_2C\underline{H}_3$); 2.20 (3H, s, $NCOCH_3$); 2.24 (1H, dt, Hβ-3); 2.49 (1H, ddd, Hα-3); 3.48 (1H, m, $OC\underline{H}_xH_yCH_3$); 3.57 (2H, broad, $NC\underline{H}_2CH_3$); 3.71 (1H, ddd, H-4); 3.78 (1H, m, $OCH_x\underline{H}_yCH_3$); 5.20 (1H, dd, H-2); 5.78 (1H, d, H-5); 7.20 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 1660 (C=O) str.,
Ms (m/e). 305[M]+, 259, 228, 190, 161, 147, 130, 91, 83, 70, 43, 32.
Accurate mass: calculated for $C_{17}H_{23}NO_2S$ 305.1449; found: 305.1447.

Compounds 8a and 8b. Prepared as above. A solution of N-ethylthiocinnamamide (2.0g;10.5mmol), N-methyl maleimide (1.28g; 11.5mmol) and pyridine (1.7ml; 21.0mmol) in acetone (20ml) was treated with a solution of acetyl chloride (1.5ml; 21.0mmol) in acetone (20ml). Aqueous work-up, then chromatography (SiO_2; 50% ethyl acetate/hexane), gave an isomeric mixture of **8a** and **8b** as a white solid (2.15g; 60%, mp 57-60°C).
8a ^{1}H NMR ($CDCl_3$), δ: 0.95 (3H, t, $NCH_2C\underline{H}_3$); 1.94 (3H, s, $COCH_3$); 2.83 (3H, s, NCH_3); 3.10 (1H, m, $NC\underline{H}_xH_yCH_3$); 3.72-3.87 (3H, m, $NCH_x\underline{H}_yCH_3$, H-3, H-4); 4.23 (1H, d, H-2); 7.39 (2H, dm, C4-Ph *ortho* protons).
8b ^{1}H NMR ($CDCl_3$), δ: 1.00 (3H, t, $NCH_2C\underline{H}_3$); 1.87 (3H, s, $COCH_3$); 2.98 (3H, s, NCH_3); 3.36 (1H, m, $NC\underline{H}_xH_yCH_3$); 3.62 (1H, m, $NCH_x\underline{H}_yCH_3$); 3.62 (1H, dd, H-3); 4.22 (1H, d, H-2); 4.32 (1H, dd, H-4); 6.19 (1H, d, H-5); 7.43 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3100-3000 (C-H) aromatic str., 3000-2800 (C-H) aliphatic str., 1700, 1650 (C=O) str., 1600 (C=C) str.
Ms (m/e). 344[M]+, 311, 233, 190, 161, 147, 130. 103, 86, 77, 57, 43.
Accurate mass: calculated for $C_{18}H_{20}N_2O_3S$ 344.1194; found: 344.1192.

Compounds 9a and 9b. Prepared as above. A solution of thiocinnamamide (3.0g; 18.4mmol), N-methyl maleimide (2.25g; 20.2mmol) and pyridine (30ml; 36.8mmol) in acetone (25ml) was treated with a solution of acetyl chloride (2.62ml; 36.8mmol) in acetone (25ml). Aqueous work-up, then chromatography (SiO_2; 50% ethyl acetate/hexane), gave an isomeric mixture of **9a** and **9b** as a white solid (4.0g; 61%, mp 60-62°C).
9a ^1H NMR ($CDCl_3$), δ: 2.28 (6H, s, $N(COCH_3)_2$); 2.92 (3H, s, NCH_3); 3.73 (1H, dd, H-4); 3.85 (1H, dd, H-3); 4.21 (1H, d, H-2); 6.58 (1H, d, H-5); 7.41 (2H, dm, C4-Ph *ortho* protons).

9b ^1H NMR ($CDCl_3$), δ: 2.23 (6H, s, $N(COCH_3)_2$); 3.00 (3H, s, NCH_3); 3.71 (1H, dd, H-3); 4.17 (1H, d, H-2); 4.38 (1H, dd, H-4); 6.34 (1H, d, H-5); 7.37 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3060 (=C-H) vinylic str., 3100-3000 (C-H) aromatic str., 1690 (C=O) str., 1600 (C=C) str.
Analysis: calculated for $C_{18}H_{18}N_2O_4S$: C, 60.32%, H, 5.06%, N, 7.82%; found: C, 60.09%, H, 5.28%, N, 7.79%.
Ms (m/e). 358[M]+, 316, 274, 205, 162, 130, 113, 91, 77, 54, 43.
Accurate mass: calculated for $C_{18}H_{18}N_2O_4S$ 358.0987; found: 358.0980.

Compound 10. Prepared as above. A solution of N-ethyl thiocinnamamide (230mg; 1.2mmol), cyclopentene (117μl; 1.325mmol) and pyridine (195μl; 2.4mmol) in acetone (10ml) was treated with a solution of acetyl chloride (171μl; 2.4mmol) in acetone (10ml). Aqueous work-up, then chromatography (SiO_2; 50% ethyl acetate/hexane), gave **10** (312mg; 86%, oil).
^1H NMR ($CDCl_3$), δ: 1.14 (3H, t, $NCH_2C\underline{H}_3$); 1.55-1.83 (4H, m, H_α-7, H_x-8, H_2-9); 1.87-2.03 (2H, m, H_β-7, H_y-8); 2.15 (3H, s, $COCH_3$); 2.15 (1H, m, H-3); 3.44 (1H, t, H-4); 3.50 (1H, m, H-2); 3.50 (1H, dq, $NC\underline{H}_xH_yCH_3$); 3.65 (1H, dq, $NCH_x\underline{H}_yCH_3$); 5.80 (1H, d, H-5); 7.17 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3060 (=C-H) vinylic str., 3100-3000 (C-H) aromatic str., 3000-2800 (C-H) aliphatic str., 1690 (C=O) str., 1595 (C=C) str.
Ms (m/e). 301[M]+, 233, 190, 147, 130, 91, 70, 43, 28.

Compound 11. Prepared as above. A solution of thiocinnamamide (875mg; 5.37mmol), cyclopentene (520μl; 5.9mmol) and pyridine (865μl; 10.7mmol) in acetone (20ml) was treated with a solution of acetyl chloride (760μl; 10.7mmol) in acetone (20ml). Aqueous work-up, then chromatography (SiO_2; 50% ethyl acetate/hexane), gave **11** (800mg; 47%, mp 72-74°C).
^1H NMR ($CDCl_3$), δ: 1.55-1.85 (4H, m, H_α-7, H_x-8, H_2-9); 1.9-2.1 (2H, m, H_β-7, H_y-8); 2.26 (1H, m, H-3); 2.47 (6H, s, $N(COCH_3)_2$); 3.48 (1H, t, H-4); 3.62 (1H, m, H-2); 5.95 (1H, d, H-5); 7.31 (2H, dm, C4-Ph *ortho* protons).
IR (cm^{-1}): 3060 (=C-H) vinylic str., 3100-3000 (C-H) aromatic str., 3000-2800 (C-H) aliphatic str., 1690 (C=O) str., 1595 (C=C) str.
Ms (m/e). 315[M]+, 273, 272, 204, 162, 161, 43.
Accurate mass: calculated for $C_{18}H_{21}NO_2S$ 315.1291; found: 315.1289.

References and notes

1. On leave from the NMR laboratory of the Institute for General and Analytical Chemistry, Technical University, H-1521 Budapest, Hungary.
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5. It should be noted that for a number of compounds the yields quoted in Table 1 differ from those reported in an earlier communication (see ref. 6.). This appears to be due to increasing the scale of the reactions.
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8. Molecular models were constructed with standard bond lengths using the Chem-X suite of programs developed and distributed by Chemical Design Ltd, Oxford, England. The structural parameters for the thioamide moieties were obtained from: Ann Kerr, K; Van Roey, P. M. A. O. *Acta Crystalographica,* **1968**, 1250.
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12. Salem has shown this type of transition state involving four points of interaction to be important - see ref. 9.
13. COSY spectra were recorded for compounds **6**, **7**, **8**, **9**, **10**, **11**; HETCOR experiments were carried out for compounds **5**, **7**, **8**, **9**, **10**, **11**.
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