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GENERATION AND CYCLOADDITIONS OF 2-(N-ACYLAMINO)-1-THIA-1,3-DIENES. STRUCTURAL INVESTIGATIONS USING NMR METHODS. PART I.

Ian T. Barnish,[b] Colin W. G. Fishwick,[a*] David R. Hill[a] and Csaba Szantay Jr.[a,†]

[a] The University of Leeds, School of Chemistry, Leeds LS2 9JT, U. K.

[b] Pfizer Central Research, Sandwich, Kent CT13 9NJ, U.K.

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Abstract - A method has been developed for the efficient generation of 2-(N-acylamino)-1-thia-1,3-dienes. These novel hetero-dienes, which are generated via acylation of the corresponding thioamides, undergo irreversible regio- and stereospecific Diels-Alder addition to the starting thioamides to yield 6-(N-acylamino)-3,4-dihydro-2*H*-thiopyrans. The regiochemistry, relative configurations and the major solution conformations of the thiopyrans **4a-c** and **10** have been determined using NMR techniques.

In addition, it has been found that these systems exhibit a number of unique physical and chemical properties.

The Diels-Alder reaction is one of the most powerful methods available for the regio- and stereoselective construction of six-membered ring systems.[2] Recently, the hetero Diels-Alder reaction, where the diene or dienophiles contain one or more heteroatoms, has seen extensive use for the synthesis of heterocyclic ring systems.[3] However, the majority of examples involving the use of a hetero-diene component are concerned with aza- or oxa- analogues, whilst only a limited number of Diels-Alder reactions involving 1-thiadienes has been reported. For instance, certain thioaldehydes (e.g. 3-methyl-1-thia-1,3-diene)[4] and thioketones (e.g. 2,4-diphenyl-1-thia-1,3-diene)[5] undergo Diels-Alder dimerization to yield the corresponding 3,4-dihydro-2*H*-thiopyrans.

Thiopyran rings are useful synthetic intermediates and can be transformed into a number of structurally important systems, notably cyclopentenes via Ramberg - Bäcklund type methodologies.[6] Clearly the characteristic regio- and stereocontrol associated with the Diels-Alder reaction makes it an attractive route to these useful synthetic intermediates. Reports concerning the cycloadditions of more functionalized and thus more synthetically useful thiadienes, however, are rare. Brunskill and co-workers have reported[7] that certain 3-aryl-2-cyanothioacrylamides exist in equilibrium with the [4+2] dimers at room temperature. It has also been shown that these heterodienes can undergo cycloaddition with other dienophiles.[8]

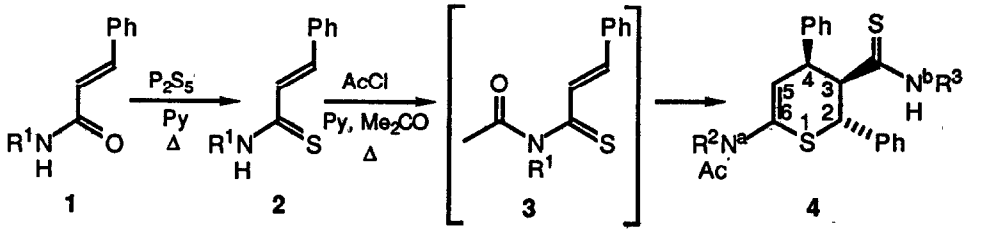
In this paper we describe the first examples of the generation of 2-(N-acylamino)-1-thia-1,3-dienes, which can be formed via acylation of thioamides and which undergo facile and irreversible regio- and stereospecific Diels-Alder cycloaddition to the starting thioamides to yield usefully functionalized

3,4-dihydro-2*H*-thiopyrans. In a forthcoming paper we also describe similar cycloadditions to a range of other dienophiles, and rationalize the observed regio- and stereoselectivities in terms of frontier molecular orbital interactions.

Results and Discussion

Synthesis

The thioamide precursors **2** are readily prepared by reaction of P_2S_5 with the corresponding amides **1**. Acetyl chloride (2 equivs.) is then added to a solution of thioamides **2** in a pyridine/acetone mixture at 60°C, and this solution heated for 18 hrs. Aqueous workup followed by chromatography of the resulting dark red oils yields thiopyrans **4**, presumably via [4+2] cycloaddition involving N-acylamino thiadienes **3** (Scheme 1).

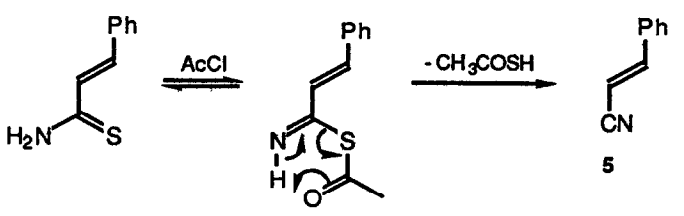


a, $R^1 = H$, $R^2 = R^3 = Ac$

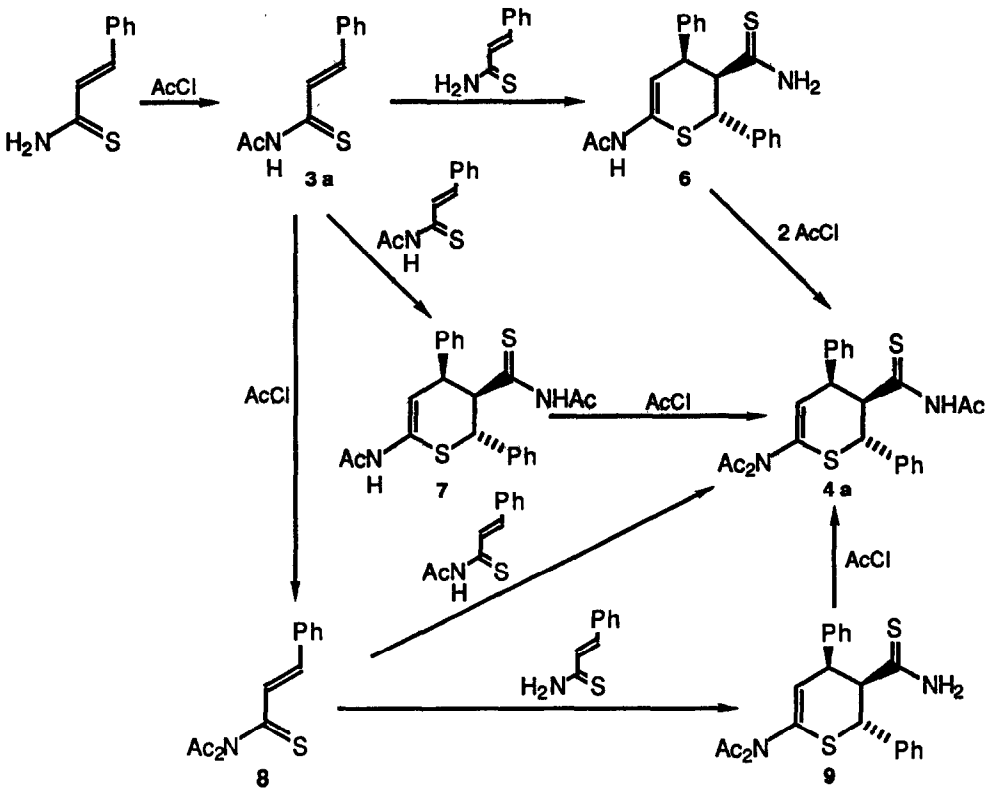
b, $R^1 = R^2 = R^3 = Et$

SCHEME 1

Increasing or decreasing the temperature or the relative amount of acetyl chloride did not increase the yields of thiopyrans **4**. In the case of thiocinnamamide **2a** a substantial amount of cinnamonitrile **5** in addition to the thiopyran **4a** was obtained. The nitrile presumably results from competing S-acylation followed by elimination of thioacetic acid:

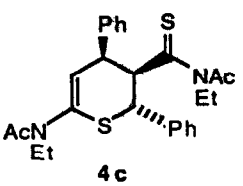


It is noteworthy that in the case of thiocinnamamide, the triacetylated derivative **4a** is obtained as the exclusive thiopyran product. This product may arise via acylation with excess acid chloride of cycloadduct **6**, resulting from cycloaddition of N-acylamino diene **3a** with thiocinnamamide. Alternatively, formation of **4a** could occur via dimerization of **3a** to yield **7**, followed by acylation. A third possibility is *in situ* acylation of diene **3a** to yield the N,N-bis-acylamino diene **8**, followed by either addition to **3a**, or to thiocinnamamide followed by acylation of **9** (Scheme 2).



SCHEME 2

Thiopyran **4c** was isolated as by-product from the cycloaddition of thioamide **2b** with cyclopentene (discussed in a forthcoming paper). However, due to its structural similarity to thiopyrans **4a-b**, we include this compound in the following discussion.[9]



4c

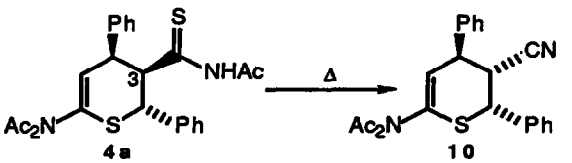
As in the case of **4a**, **4c** may result from cycloaddition of N-acylamino thioamide **3b** with starting thioamide **2b** followed by N-acylation, or directly from dimerization of **3b**.

In all cases the Diels-Alder reactions are regio- and stereospecific, resulting in the *endo* cycloadducts. This is consistent with earlier observations concerning the cycloadditions of other 2- and 4- hetero- substituted 1-thia-1,3-dienes.[10,11]

As mentioned earlier, certain α,β-unsaturated thioamides have been shown to exist in equilibrium with their [4+2] dimers at room temperature. However, in our case, even after prolonged heating of thioamides **2**, no dimeric products could be isolated and the thioamides were completely recovered. In addition, NMR examination of a solution of thioamide **2a** in a mixture of pyridine and acetone at a range of different temperatures (60°C, 25°C and -30°C) revealed only the presence of the thioamide, and no dimeric system could be detected. These results are consistent with the generation of the N-acylaminothiadienes as the reactive intermediates, and the possibility of the thiopyrans **4** being derived from *in situ* acylation of the dimeric thioamides is unlikely.

MO calculations[12] indicate a decrease in the separation of the HOMO-LUMO energy of 11 kcal/mol in going from thioamide to the N-acylated systems, thus accounting for the facile and irreversible nature of these cycloaddition reactions.

Interestingly, heating thiopyran **4a** in both polar and non-polar solvents gave the nitrile **10**, in which the configuration at C-3 has undergone complete inversion, in essentially quantitative yield (*vide infra*).



4a **10**

Structure Determinations

The constitutions, relative configurations and some conformational features of compounds **4a-c** and **10** were investigated by NMR methods employing the concerted use of one-dimensional (1D) $^{1}H\{^{1}H\}$ and $^{13}C\{^{1}H\}$ NOE difference experiments together with ^{13}C-^{1}H (HETCOR) shift correlated 2D spectra. In order to maintain a rigorous approach in deducing the structures of the thiopyrans, no *a priori* assumptions about the expected regio- or stereocontrol of the corresponding Diels-Alder reactions were made, as the possibility of epimerization during or after the reactions could not be ruled out. Conceptually, the structure elucidations involved the following steps.

First, most signals in the ^{1}H NMR spectra of **4a-c** and **10** can be readily assigned. The H-5 doublet is easily identified owing to its low-field chemical shift, and serves as a convenient starting point for

tracing the H-5, H-4, H-3, H-2 coupling network in the thiopyran ring. The ethyl subsystems (in compounds **4b** and **4c**) were identified by homo-decoupling experiments. Also, at this stage, HETCOR spectra unambiguously gave the assignment of the H-bearing carbons (with the exception of the aromatic CH carbons which are correlated to the crowded Ph ^{1}H region). (Full ^{1}H shift characterizations are given in the experimental section; for convenience, characteristic ^{1}H chemical shifts and vicinal coupling constants are also collected in Table 1; selected ^{13}C chemical shifts are listed in Table 4).

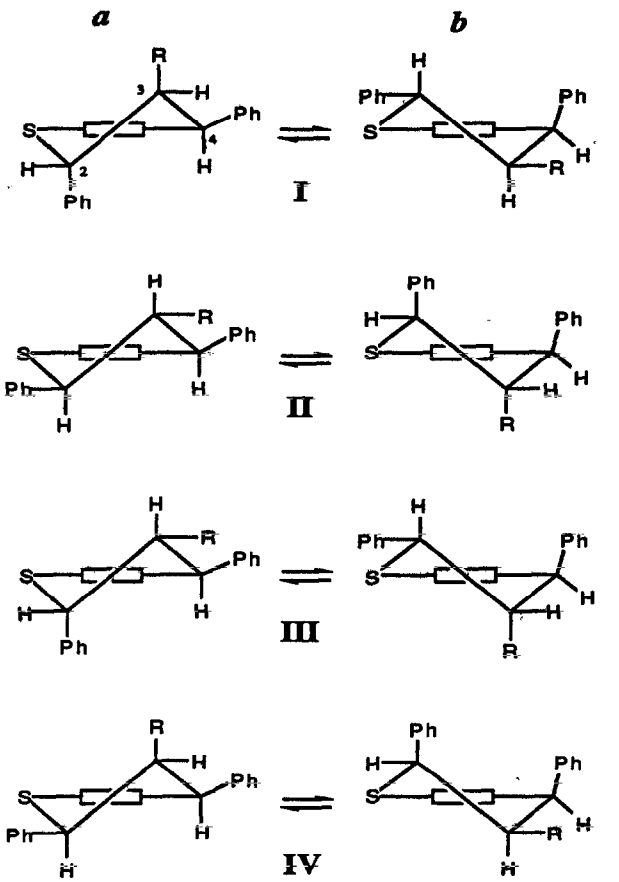
Secondly, a distinction between the two possible regioisomers associated with the corresponding Diels -Alder reactions had to be made. This question was resolved by ^{13}C{^{1}H} selective NOE difference measurements. This experiment exploits the fact that low power irradiation of suitably separated ^{1}H signals results in an NOE enhancement in the neighbouring quaternary carbons positioned two bonds from the irradiated protons.[13] Irradiation of the H-2 and H-3 signals is thus expected to enhance the neighbouring quaternary carbon of the C-2 and C-3 substituent, respectively. Since for compounds **4a-c** and **10** the corresponding quaternary carbons (C=S, CN and the Ph-*ipso* carbons) resonate in markedly different and characteristic chemical shift ranges, both experiments independently identify the regioisomer in hand. Normally, the irradiation of H-4, resulting in the enhancement of the C-4 Ph *ipso* carbon, was also carried out as a control experiment. (Results of the heteronuclear NOE measurements are indicated in Table 4).

Finally, ^{1}H{^{1}H} NOE difference measurements were performed, which served a three-fold purpose: *a)* to establish the relative configurations and the predominant or preferred conformations of the thiopyran ring, independently from the somewhat limited stereochemical information provided by the vicinal (H,H) couplings (Table 1), *b)* to clarify the remaining constitutional ambiguities concerning the assignment of the Ac group(s) to specific N sites (in **4a,b**); *c)* to complete the ^{1}H assignments. [The C-2 and C-4 Ph *ortho* protons (hereafter referred to as "o-2" and "o-4") in particular, are concealed among the non-first-order aromatic ^{1}H signals at 400 MHz, but are readily located by irradiation of the H-2 and H-4 protons, respectively]. Moreover, the NOE measurements revealed an unexpected saturation transfer between the H-2 and H-3 protons in compounds **4a** and **4c** (*vide infra*). Results of the homonuclear NOE experiments, together with a list of the stereochemically diagnostic through-space connectivities reflected by them, are collected in Table 2.

Stereochemical deductions were based on the consideration of all four possible diastereoisomers and the two main half-chair conformations of the thiopyran ring, as illustrated in Scheme 3. Each individual stereostructure in Scheme 3 can be characterized by a unique combination of "short" and "long", structurally diagnostic d(i;j) H-i,H-j interproton distances. (In this context, "short" refers to a spatial H-H arrangement which should allow the development of readily detectable steady-state NOEs, while "long" corresponds to a distance through which no appreciable first-order enhancements are expected

Table 1. ^1H chemical shifts ($CDCl_3$) δ(ppm) and $^3J(H,H)$ vicinal coupling constants (Hz) of the ring-protons in compounds 4a-c and 10.

	4a		4b		4c		10	
	δ	J	δ	J	δ	J	δ	J
H-2	4.85		4.57		4.91		4.63	
		11.3		11.9		10.9		7.2
H-3	5.31		4.23		4.75		3.45	
		4.5		4.6		4.3		4.6
H-4	4.18		4.38		4.39		3.85	
		6.5		6.2		6.7		4.0
H-5	6.08		5.93		6.03		6.00	



SCHEME 3

Table 2. Results of the 1D $^1H\{^1H\}$ NOE difference experiments on compounds **4a-c** and **10** carried out in $CDCl_3$. [The measured NOE intensities are arbitrarily denoted as "s" (strong, >8%), "m" (medium, 3-8%) and "w" (weak, 1-3%)].

compound	irradiated proton	observed enhancements H-2	H-3	H-4	H-5	o-2[a]	o-4[a]	other	*stereostructurally diagnostic short distances:*
4a	H-2	*	*b*	-	-	s	s	N^bH(w)	d(2;o-4); d(3;4); d(3;o-2)
	H-3	*b*	*	s	-	s	-	N^bH(w), N^bCOMe(w)	
	H-4	-	s	*	s	-	s		
	H-5	-	-	s	*	-	m		
	o-2	m	m	-	-	*	-		
	o-4	m	-	m	w	-	*		
	N^bH	m	w	-	-	w	w	N^bCOMe(s)	
	$N^b(COMe)_2$	-	-	-	w	-	-		
4b	H-2	*	-	-	-	s	s	N^bH(s)	d(2;o-4); d(3;4); d(3;o-2)
	H-3	-	*	s	-	s	-	N^bH(w)	
	H-4	-	s	*	s	-	s		
	H-5	-	-	m	*	-	w	N^aCOMe(w)	
	N^bH	s	w	-	-	-	-	N^bCH_2Me(s)	
	N^aCOMe	-	-	-	w	-	w		
4c	H-2	*	*c*	-	-	s	s		d(2;o-4); d(3;4); d(3;o-2)
	H-3	*c*	*	s	-	s	-		
	H-4	-	s	*	s	-	s		
	N^aCOMe	-	-	-	w	-	w		
	N^bCOMe	-	-	-	-	-	-	N^bCH_2Me (w)(w)	
10	H-2	*	m	-	-	s	m		d(2;3); d(2;o-4); d(3;4); d(3;o-2); d(3;o-4); [d(4;o-2)]
	H-3	m	*	s	-	m	w		
	H-4	-	s	*	s	w	s		
	H-5	-	-	m	*	-	m	$N^a(COMe)_2$(w)	
	o-2	m	m	w	-	*	-		
	o-4	m	w	m	w	-	*		

a) o-2 And o-4 refer to the C-2 Ph and C-4 Ph *ortho* protons, respectively. *b)* -3% at 25 °C, zero at 50 °C and - 20% at - 30°C in $CDCl_3$; - 20% in DMSO at room temperature. *c)* -14% at 25 °C and -4% at 50 °C.

to be observed). In order to allow a straightforward interpretation of the NOE results in relation to the appropriate stereochemical possibilities, these distance-combinations are listed in Table 3. A comparison of the observed NOE connectivities with Table 3 readily defines the relative configuration and the preferred conformation of the thiopyran ring for each Diels-Alder adduct. (It is noteworthy that without limiting the number of structural possibilities by the preliminary knowledge of regioaddition provided by the $^{13}C\{^1H\}$ NOE experiments, the homonuclear NOE measurements alone were not sufficient to establish unambiguously *both* the stereo- and regiostructures).

Table 3. Unique combinations of "short" (S) and "long" (L) d(i;j) H-i--H-j interproton distances for the stereostructures shown in Scheme 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.

	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
d(3;o-2)	S	S	S	S	L	S	S	L
d(4;o-2)	S	L	L	L	S	L	L	L

[a] o-2 and o-4 denote the C-2 Ph and C-4 Ph *ortho* protons, respectively.

Table 4. Characteristic ^{13}C chemical shifts δ(ppm) ($CDCl_3$) for compounds **4a-c** and **10**.

Carbon No.:		4a	4b	4c[d]	10
C-2		45.6	43.7	48.7	45.7
C-3		54.4	59.7	56.7	38.9
C-4		45.4	45.9	45.4	41.0
C-5		126.3	124.1	125.1	124.8
C-6	*irr:*	133.6	136.5	136.2	134.2
C-4Ph[a]	*(H-4)*	137.3	138.8	139.5	137.7
C-2Ph[a]	*(H-2)*	138.1	136.3	138.9	137.1
other	*(H-3)*	208.1[b]	199.5[b]	210.9[b]	117.7[c]

[a] Ph *ipso* carbon; [b] -CS-; [c] -CN; Underlined characters denote the signals observed in the selective $^{13}C\{^1H\}$ NOE experiments upon irradiation of the proton multiplets indicated in italics in the same rows. [d] For this compound, the irradiation of H-3 also gave an enhancement on the N^bCOMe carbonyl, as well as a transferred NOE on the C-2Ph *ipso* carbon (see text and Figure 1).

For compound **4a**, inspection of the ^1H, ^{13}C and HETCOR spectra shows, as a main feature, the presence of the CH-5(olefinic), CH-4(aliphatic), CH-3(aliphatic), CH-2(aliphatic) subsystem. This, together with all the other obvious characteristics of the ^1H and ^{13}C spectra (showing, notably, the presence of two equivalent and one separate Ac groups, and a thiocarbonyl group giving a typically low-field ^{13}C signal at δ 208.1) readily accounts for the gross constitution of the molecule: the 2,3,4,6-substituted thiopyran ring with a Ph in the C-4 position, an NHAc or $N(Ac)_2$ on C-6 and, according to the two possible regioisomers, a CSNHAc or $CSN(Ac)_2$ on C-3 or C-2, and a Ph on C-2 or C-3.

In the selective heteronuclear NOE difference spectra, irradiation of H-2 gave an enhancement on one of the aromatic *ipso* carbon signals (δ 138.1), readily proving the presence of a Ph group in the C-2

position, and therefore placing the thioamide unit on C-3. [The experiment also differentiates between the two closely spaced C-4 Ph and C-2 Ph quaternary carbon signals (see Table 4)]. As control experiments, H-4 and H-3 were also irradiated, and gave the expected enhancements on the C-4 Ph *ipso* carbon (δ 137.3) and C-3 thiocarbonyl carbon (δ 208.1), respectively.

The $^{3}J(2,3)$=11.3 Hz and $^{3}J(3,4)$=4.5 Hz couplings accord with a *trans*-diaxial and *synclinal* relationship for the relevant proton-pairs, respectively. Clearly, this geometry is manifested in structure "**Ib**" (Scheme 3) only, and is independently identified by the homonuclear NOE results (cf. Tables 2 and 3). Furthermore, the NOE connections of the $N^{b}H$ proton to H-3 and H-2 on the one hand, and the enhancement detected on H-5 when irradiating $N^{a}(COMe)_2$ on the other, clearly prove that the N^{b} nitrogen is mono-, while N^{a} is bis-acylated. The "**Ib**" conformation is apparently predominant, which can be explained by the steric strains associated with the two axial C-2 and C-3 substituents in "**Ia**".

The structural arguments based on the presented NMR information for compounds **4b** and **4c** (see Tables) are entirely analogous to those discussed for **4a**, readily proving their regiochemistry (see the results of the $^{13}C\{^{1}H\}$ NOE experiments in Table 3) and predominant "**Ib**" geometry. (As a representative example, results of the $^{13}C\{^{1}H\}$ NOE experiments for **4c** are shown in Figure 1). In **4b**, the short d(3;NH), d(2;NH), d(4;NH) and d(5;COMe) distances reflected by the homonuclear NOE experiments clearly place the acyl group on the N^{a} nitrogen.

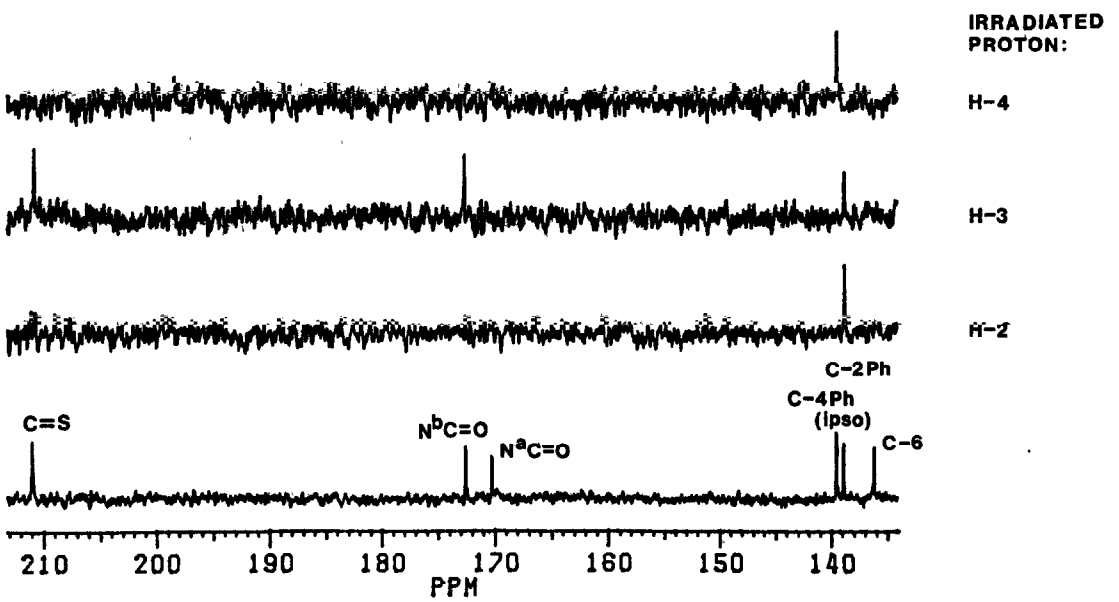


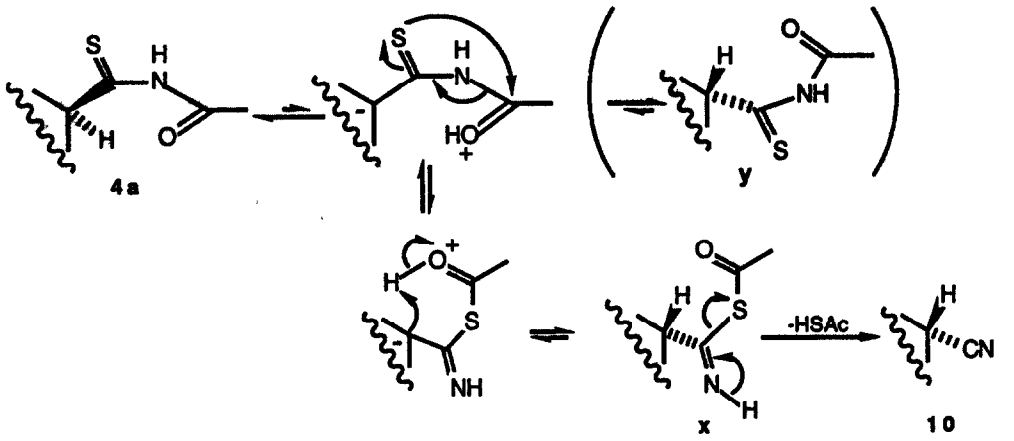
FIGURE 1. The quaternary carbon region of the broad-band ^{1}H decoupled ^{13}C spectrum (bottom trace) of **4c**, and $^{13}C\{^{1}H\}$ NOE difference spectra obtained via the selective irradiation of the H-2, H-3 and H-4 signals, respectively. Note the enhancement observed (in addition to that seen on the C=S carbon) on the $N^{b}C$=O signal upon irradiating H-3, and also the transferred NOE on the C-2 Ph *ipso* carbon in the same experiment - see text.

Compound **10** is gradually formed upon heating **4a**. The nitrile functionality of **10** is readily apparent by reference to the ^1H and ^{13}C spectra, the latter, in particular, showing the very characteristic ^{13}CN signal at δ 117.7. Also, the $^3J(H,H)$ couplings (Table 1) in **10** indicate a drastic change in geometry with respect to **4a**. It is noted that, for the sake of rigour, the possibility of regioisomerization through a retro- Diels-Alder process during the formation of **10** could not be entirely ruled out. However, the results of the $^{13}C\{^1H\}$ NOE measurements (Table 4) clearly identify the (unaltered) regiochemistry of **10**. The relatively small $^3J(2,3)$ and $^3J(3,4)$ couplings accord with *synclinal* arrangements for the respective protons. This alone provides only a small limitation in the number of stereostructural possibilities in Scheme 3 (excluding only "**Ib**", "**IIa**" and "**IIIa**"). In the homonuclear NOE measurements, however, the short d(2;3), d(2;o-4), d(3;4), d(3;o-2), d(3;o-4) distances unambiguously identify the diastereoisomer as being "**III**", with a preferential "**b**" conformation (cf. Tables 2 and 3). The presence of the weak H-4--o-2 NOE interaction on the other hand indicates a small contribution of "**IIIa**" in the conformational equilibrium. In the preferred "**IIIb**" geometry of **10** the C-3 substituent avoids much of the steric repulsion with the C-4 Ph present in **4a** ("**Ib**"), which can explain the driving force for the C-3 epimerization.

Further chemical and structural considerations

Conversion of **4a** *into* **10**

The **4a**–>**10** conversion process is essentially quantitative within ca. three days at 65 °C in $CDCl_3$. Heating to 140°C in DMSO-d_6 induces the transformation to take place within a few minutes. (The process could be conveniently monitored in the NMR tube). In this regard, the following should be noted: *a)* throughout the **4a**–>**10** process, the β-nitrile isomer of **10** was never observed; *b)* in order to investigate whether any external protons participate in the process, several attempts were made to exchange H-3 with deuterium by heating **4a** in the presence of CD_3OD as well as in DMSO-d_6/D_2O solutions. However, in neither case was any exchange observed, indicating a **4a**–>**10** conversion in which no external proton source is required. (Moreover, the **4a**–>**10** conversion also proceeds easily, although more slowly, in dry benzene). To substantiate further this aspect of the process, an analogue of **4a**, **4a(d)**, deuterium labeled selectively on C-3, was prepared.[14] Upon heating **4a(d)** at 140°C in DMSO-d_6 /H_2O, the conversion into C-3 epimeric nitrile took place with complete deuterium retention on C-3; *c)* neither epimerization nor CN formation was found to occur in **4b**, even after heating to 140 °C in DMSO. These findings suggest that both processes are heavily dependent on the presence of the N^bAc group, and are intimately interrelated. A possible mechanism which may account for the above observations is the following:[15]



Clearly, in order to accommodate our observations concerning the lack of any measurable exchange of the C-3-H proton, the relative rates of the steps in the above scheme must be fast.[16]

Conformation of the C-3 side chains

In **4b**, there is a pronounced H-2---HN^b NOE connection (a 14 % enhancement is seen on H-2 when the N^{b}H proton is irradiated). This points to the presence of a significant population of a conformation of the C-3 substituent involving a short d(2;N^{b}H) distance.[17] From model considerations, this conformation can only be associated with a nearly eclipsed (*"syn"*) relation between H-3 and C=S. On the other hand, the corresponding H-2--N^{b}H NOE interaction is much weaker in **4a** (giving a 4% NOE on H-2 upon irradiation of the N^{b}H proton)[18], showing that in this case the *"anti"* conformer must be appreciably populated at the expense of the *syn* form, thus increasing the average d(2;NH) distance relative to that in **4b**. In order to try to rationalize these observations, molecular mechanics (MM) calculations using the potential function of Weiner et al.[19] have been carried out. The resultant lowest - energy structures in **4b** and **4a** for the *syn* and *anti* isomers, respectively, are shown in Figure 2.[20] As expected in **4a**, the *"cis-trans"* or *"trans-cis"* arrangements of the CSN^{b}HAc unit provide the lowest energies. **4a**^{1} And **4a**^{2} are the two most stable structures relative to all other nearly-coplanar configurational isomers of the C-3 substituent (regardless of being in the *syn* or *anti* forms). Other isomers have distinctly higher calculated energy values and will make only slight or negligible contribution to the isomeric equilibrium. In the case of **4b**, structures **4b**^{1}and **4b**^{2} represent the preferred staggered rotamers around the N^b--Et bond (according to the calculations, other rotamers may have slight contributions to both the *syn* and *anti* forms of **4b**, but these are insignificant in the context of our considerations).

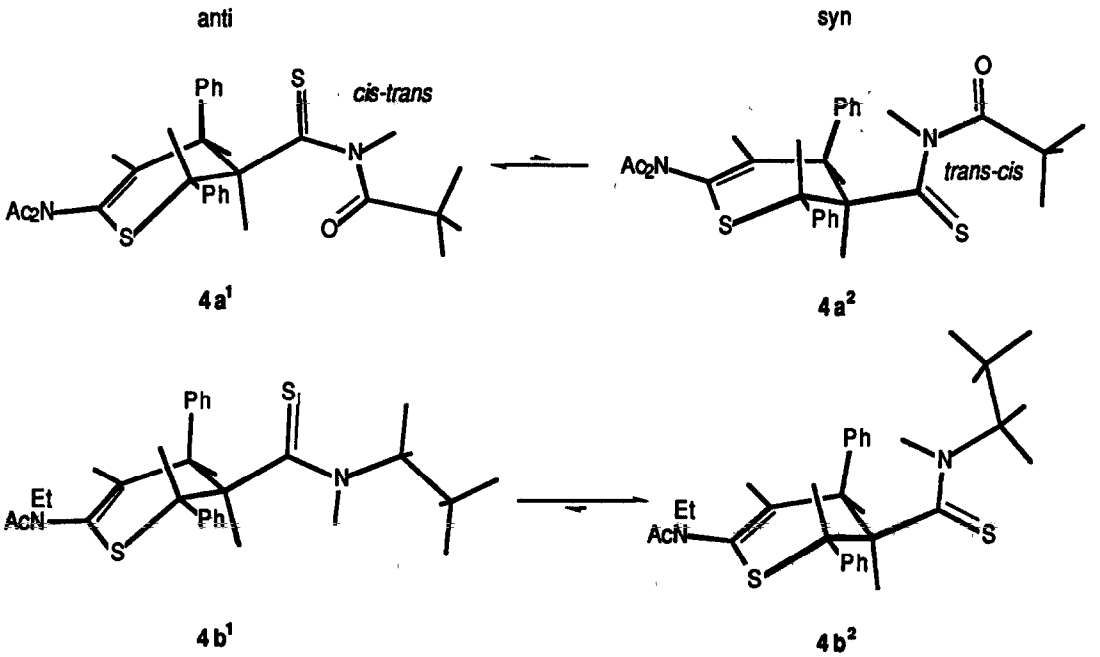
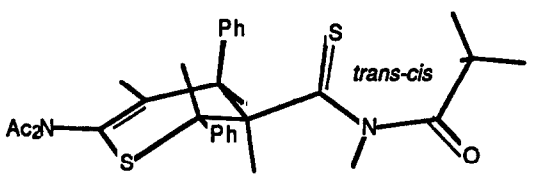


Figure 2. The most stable *anti* and *syn* conformers of compounds **4a** and **4b**, calculated by MM energy-minimizations. To aid clarity, unlabelled bonds denote H.

In **4b** there is a calculated enthalpy difference of 2.9 kcal/mol between **4b1** and **4b2** in favour of the *syn* isomer which, from the population ratio $N_{syn}/N_{anti} = \exp(-\Delta H/RT)$, gives a ca. 99 % preference of the *syn* over the *anti* conformer at room temperature, in accordance with the observed strong H-2–HN^b NOE connection. The weak NOE interaction between N^bH and H-3 on the other hand reflects the slight contribution of **4b1**. In contrast, in **4a** the *anti* conformer **4a1** is calculated to be favoured by 1 kcal/mol over the *syn* isomer **4a2**; this corresponds to a ca. 85% preference of **4a1** relative to **4a2**, in good qualitative agreement with the H-2--HN^b NOEs being significantly weaker in **4a** than in **4b**. Moreover, in **4a** the presence of a measurable contribution of the *trans-cis* arrangement of the CSN^bHAc group in the *anti* conformer (**4a3**) is reflected by the observed weak H-3-- HN^b NOE connection (**4a3** is calculated to have only ca.1% contribution relative to **4a2**).



4a3

The close proximity of the H-3 proton and the N^bAc oxygen in **4a**^{1} may involve an internal electrostatic interaction[21] between them, allowing for a rapid tautomeric equilibrium in which H-3 protonates the AcN^b oxygen and a C-3 carbanion is formed. This would provide the basis of the **4a**-->**10** conversion discussed above. The preferential population of **4a**^{1} may thus be related to the inclination of C-3 to epimerize during nitrile formation. However, for the MM calculations, no positive charge was attributed to the H-3 proton, showing that the observed difference in the rotameric population distribution around the C-3--CS bond between **4b** and **4a** is *not* caused by an attractive electrostatic H-3···O=CN^b interaction in **4a**. This "shift" towards the *anti* form in **4a** can, however, be rationalized by the following considerations. The fact that **4a**^{1} is markedly more stable than **4a**^{3} (both are in the *anti* form) indicates that the *cis-trans* arrangement of the CSN^bHAc moiety is intrinsically more favourable than the *trans-cis* arrangement (presumably because of the C=S<-->Me repulsion encountered in the latter case). On the other hand, **4a**^{2} is calculated to be greatly favoured over **4a**^{3} (both are in the *trans-cis* form), while **4b**^{2} is seen to be preferred relative to **4b**^{1}. These observations suggest that, when comparing very similar geometrical arrangements of the CSN^bHR units, the *syn* conformer is inherently more stable than the *anti*, presumably to avoid the C=S<-->Ph(C-4) repulsion associated with the *anti* isomer. It can thus be argued that in the *syn* conformer of **4a** the most favoured *cis-trans* arrangement of the C-3 side chain would involve severe N^bAc<-->H-2 and N^bAc<-->Ph(C-4) steric strains, which gives preference to the *anti* isomer.

MM calculations on **4c** provided (as expected) entirely analogous results to those in **4a**, with **4c**^{1} and **4c**^{2} being the direct stereostructural analogues of **4a**^{1} and **4a**^{2}, respectively. (For this reason the calculated lowest-energy structures were not displayed in Figure 2). A notable difference, however, is an even larger energy gap between the *anti* and *syn* isomers: ΔH between **4c**^{1} (*anti*) and **4c**^{2} (*syn*) is 5.7 kcal/mol, suggesting the practically exclusive presence of the *anti* form. (This is understandable by considering that relative to **4a**, in **4c** the *syn* isomer becomes even more strained in every possible rotamer of the C-3 substituent due to the presence of the bulky N^bEt group). The anticipated predominance of the *anti* conformer in **4c** is clearly illustrated by the heteronuclear NOE experiments; the irradiation of H-3 gave, in addition to that expected on the C=S carbon, an enhancement on the N^bAc carbonyl carbon (Figure 1), showing that a short H-3--N^bC=O H--C distance prevails with considerable lifetime.[22]

A comparison of the ^1H and ^{13}C chemical shifts of compounds **4a**, **4b** and **4c** shows some noteworthy differences. In both **4a** and **4c**, the H-2 and H-3 protons are distinctly shifted downfield from their values in **4b** (Table 1). Clearly, in view of the constitutional and, as discussed above, conformational differences involving the C-3 side chains in these compounds, these shift deviations may arise as a combined result of electrical field, van der Waals, and anisotropic effects likely to be associated with the C-3 substituents. For this reason, it is difficult to arrive at straightforward

interpretations concerning the above $\Delta\delta$ ^{1}H trends. Nevertheless, considering the marked downfield shifts of the H-3 signals (+1.08 ppm in **4a** and +0.52 ppm in **4c** relative to **4b**, respectively), it seems reasonable to attribute them, at least in part, to an H-3···O=CN^b electrostatic attraction polarizing the C-3--H bond. Moreover, in **4a** δ C-3 is shifted -5.2 ppm, while in **4c** -2.9 ppm upfield from its value in **4b** (Table 4). Again, these shifts accord with the C-3--H bond being more polarized (resulting in the increased negative character of C-3) in **4a** and **4c** than in **4b**. (However, a possible contribution of a γ-steric interaction between C-3--H and the N^{b}C=O carbon in structures **4a^1** and **4c^1** to these upfield shifts cannot be ignored). It is interesting to reflect on why in **4a** the observed trend of H-3 and C-3 being oppositely shifted relative to **4b** is more pronounced then in **4c**. Indeed, considering that in **4c** the major isomer **4c^1** was seen to be appreciably more populated than **4a^1** in **4a**, as a first approximation the opposite tendency would be anticipated. (Moreover, if the above γ-steric interaction were to have a major effect on the observed $\Delta\delta$ C-3 upfield shifts, for the same reasons this alone should also lead to $\Delta\delta$ C-3 being larger in **4c** than in **4a**). However, close examination of the calculated stereostructures **4a^1** and **4c^1** reveals that, although the H-3--O=CN^b hydrogen-oxygen distances are virtually identical (2.3Å), the O-C-N^b-C torsion angle in **4c^1** is more than double (12.3°) that in **4a^1** (5.2°). This is readily explained by the steric requirements of the N^{b}Et ethyl causing an increased out-of-plane deformation of the amide system. This departure from coplanarity will decrease N lone-pair -- C=O overlap, resulting in decreased electron density at the N^{b}Ac oxygen relative to that in **4a^1**. This would result in the C-3--H bond being less polarized in **4c** than in **4a**, providing a consistent explanation for the observed decreased deshielding of H-3 and the smaller upfield shift of C-3 found in **4c**.

A further special feature of **4a** is that H-3 and C-3 both give broad signals at room temperature (25°C) at 400 and 100 MHz, respectively; at 50°C they become sharp. Moreover, a clear field-dependence is present (H-3 gives a well-defined multiplet at 90 MHz), suggesting that a chemical exchange process is involved. In view of the fact that this broadness is absent in **4c**, its precise origin is not clear. However, it may tentatively be explained by a possibly hindered rotation involving the C-3 side chain; this in turn could be coupled to the more efficient H-3···O=CN^b electrostatic attraction in **4a** and/or the amide rotational energy barriers probably being higher in **4a** than in **4c**, owing to the destabilizing effect of the N^{b}Et group (discussed previously) in the latter case.

In **4a** and **4c** the C-2 signals are shifted +1.9 ppm and +5 ppm downfield relative to **4b**, respectively. Presumably this is caused by the fact that both **4a^1** and **4c^1** lack the C-2-H<–>HN^b *γ-gauche* steric interaction present in **4b^2**, shifting C-2 upfield in **4b**. With **4c^1** being more populated than **4a^1**, the "loss" of this effect is more pronounced in **4c** than in **4a**, which might explain the larger downfield shift observed for C-2 in the former case.

Negative peaks in the NOE difference spectra of 4a and 4c

Attention should be drawn to the negative peaks observed in the homonuclear NOE difference spectra of **4a** and **4c** upon irradiating the H-2 and H-3 signals (Table 2). For **4a**, at room temperature in $CDCl_3$, the irradiation of H-3 results in a -3% negative peak on H-2, and conversely. In DMSO the effect is much larger (-20%). **4c** Exhibits even more intense negative peaks in $CDCl_3$[23] (-14%) than in the case of **4a** (Figure 3). Accordingly, in the $^{13}C\{^1H\}$ NOE experiments on **4c**, irradiation of H-3 gives an enhancement on the C-2 Ph *ipso* carbon as a result of the saturation being partially "transferred" to H-2 (Figure 1).[24]

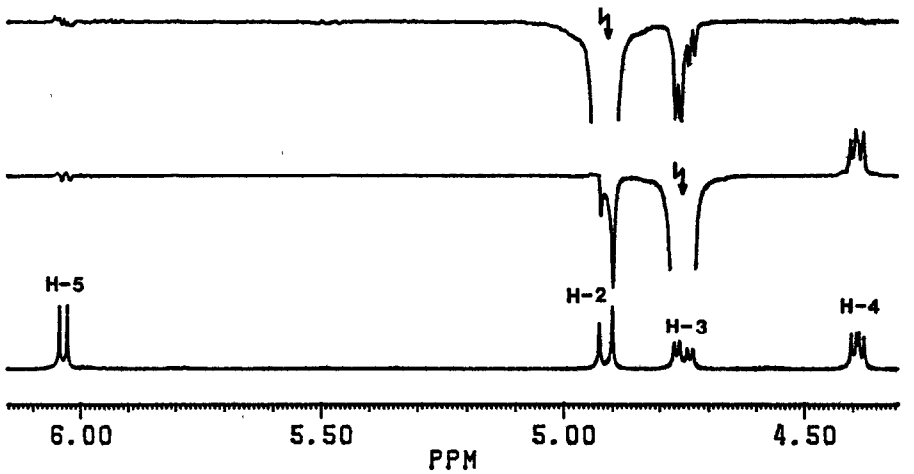


Figure 3. The ring proton region of the $^1H\{^1H\}$ NOE difference spectra obtained at room temperature for **4c**, showing negative effects on H-2 and H-3. Bottom trace shows the corresponding section of the normal proton spectrum (400 MHz, $CDCl_3$).

The observed effect couples H-2 and H-3 only, and shows a marked temperature dependence: the negative peaks gradually cease by increasing the temperature, approaching zero NOEs in accordance with the trans-diaxial relationship between H-2 and H-3. At lower temperatures, on the other hand, a prominent increase in the size of the peaks is observed (-20% in **4a** in $CDCl_3$ at -30°C).[25] The phenomenon is, however, absent in the stereochemically analogous structure **4b**, suggesting that it is related to the presence of the N^bAc group. Considering the geometry of the molecules in question, the size of the negative peaks, and the nearly first-order character of the ^1H signals involved, the possibility of three-spin-effects[26] or negative peaks due to strong couplings[27] being involved can essentially be discarded. (With the low irradiation power levels used, and the relatively large separation of the signals involved, any possibility of irradiation "spill-over" being responsible for the

observed effect can clearly be ruled out).[28] The phenomenon thus appears likely to be associated with saturation transfer via a slow chemical exchange[29] between H-2 and H-3. However, ^1H and ^2H NMR studies on the C-3-deuteriated compound **4a(d)** have conclusively shown that any possibility of a stereoselective H-2--H-3 proton transfer can be discounted. It is clear, on the other hand, that other forms of a H-2--H-3 chemical exchange in these molecules are difficult to rationalize. The phenomenon is thus recognized as being highly peculiar and unusual; further investigations to gain more insight into this problem are now in progress.

Experimental

Spectroscopy

All NMR spectra of compounds **4a-c** and **10** were recorded on a Bruker AM-400 spectrometer operating at 400.13 and 100.61 MHz for ^1H and ^{13}C nuclei, respectively, with internal deuterium lock in $CDCl_3$ and in a few cases using DMSO-d_6, DMSO-d_6/D_2O, CD_3OD and $(CD_3)_2CO$/Pyridine-d_5.The data given in the Tables and in the experimental section refer to ambient temperature (297K), unless otherwise indicated. Chemical shifts are given relative to δ_{TMS}=0.00 ppm. Two-dimensional (C-H correlated) and homonuclear NOE experiments were recorded by using the standard spectrometer software package. All NOEs were measured in non-degassed samples. For the selective $^{13}C\{^1H\}$ NOE measurements the micro-program described by Sanchez - Ferrando[13] was employed, typically using 10s pre-irradiation times and a 6 Hz exponential line-broadening before Fourier transformation. The experiments were typically accumulated overnight, and for 72 hrs in the case of irradiating H-3 in **4a**. For the homonuclear NOE experiments 4 s pre-irradiation times were used, FIDs were exponentially multiplied prior to Fourier transformation (LB = 1 - 3 Hz). Subsaturating irradiation power levels (typically 55-60L) were carefully adjusted to avoid spill-over effects to adjacent signals. ^{13}C multiplicities were determined by the APT method.[30]

The ^2H NMR spectrum of **4a(d)** was obtained at 61.4 MHz on the same instrument operating in an unlocked mode, with broad-band ^1H decoupling.

NMR spectra of precursors **1**and **2** were recorded on a Jeol FX 90Q instrument (90 MHz for ^1H and 22.5 MHz for ^{13}C).

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

Synthesis

N-Ethyl-thiocinnamamide (2b).[31] Phosphorus pentasulphide (1.27g; 5.7mmol) was added portionwise to a stirred solution of N-ethylcinnamamide (2.0g; 11.4mmol) in anhydrous pyridine (6.0ml). The resulting yellow /orange solution was heated at reflux for 35min. and then allowed to cool to room temperature. The mixture was poured into water (10ml) and then extracted with diethyl ether (3x10ml). The combined extracts were washed with dil. HCl, then water, and dried with anhydrous magnesium sulphate. After filtration, the solvent was removed by evaporation *in vacuo* giving a brown solid. Crystallisation from methanol gave gold needles (1.91g; 87.5%), mp 107-108°C. Lit. 106-107°C.
^1H NMR ($CDCl_3$), δ: 1.25 (3H, t); 3.8 (2H; dq); 6.85 (1H, d); 7.2-7.5 (5H, m); 7.8 (1H, d). ^{13}C NMR , δ: 193.8; 141.7; 134.5; 129.5; 128.6; 127.7; 127.1; 40.7; 13.0.
IR (cm^{-1}): 3150 (N-H)str.,3050 (=C-H) vinylic str. Analysis: calculated for $C_{11}H_{13}NS$: C, 69.0%, H,6.85%,

N, 7.35%, S, 16.76%, found; C, 68.9%, H, 6.75%, N, 7.05%, S, 16.85%.
Ms (m/e).191 [M]+, 147, 130, 115, 103, 91, 77, 68, 60, 51, 44.
Accurate mass: calculated for $C_{11}H_{13}NS$ 191.0769; found: 191.0765.

Thiocinnamamide (2a).[32] Prepared as for **2b** using cinnamamide (1.47g; 10mmol), phosphorus pentasulphide (1.11g; 5mmol) and pyridine (4.4ml) giving **2a** as yellow needles after recrystallisation from benzene (1.07g; 66%), mp 142-143°C. Lit. 142-142.5°C.
^{1}H NMR ($CDCl_3$), δ: 7.77 (1H, d); 7.4 (5H, m); 6.87 (1H, d); 1.65 (1H, s).
IR (cm^{-1}): 3120,3270 (N-H)str., 1630 (C=C)str., 1570 (N-H)bend, 1420 (C-N)str.
Ms (m/e). 163[M]+, 162, 129, 102, 77, 63, 51, 45.
Accurate mass: calculated for C_9H_9NS 163.0455; found: 163.0453.

Compound 4a. A solution of acetyl chloride (0.9ml; 12.3mmol) in acetone (10ml) was added dropwise to a solution of thiocinnamamide (1.0g; 6.13mmol) in pyridine (1.0ml; 12.3mmol) and acetone (10ml) at reflux. The resulting dark red solution was heated at reflux for 18h, during which precipitation of pyridinium hydrochloride was observed. The reaction mixture was allowed to cool to room temperature and poured into water (25ml). The resulting suspension was extracted with diethyl ether (3x25ml), and the combined extracts were washed with water until the aqueous layer was neutral to pH indicator. The ethereal layer was then dried with anhydrous magnesium sulphate and filtered. Evaporation *in vacuo* of the filtrate gave a dark red/brown solid which, on 'flash' column chromatography (SiO_2, 40% ethyl acetate/hexane), gave cinnamonitrile as a brown oil (0.21g; 26.5%) and **4a** as a white crystalline solid (0.56g; 40.4%), mp 81-84°C.
Ms (m/e). 452[M]+, 351, 204, 162, 130, 103, 77, 43.
Accurate mass: calculated for $C_{24}H_{24}N_2O_3S_2$ 452.1228; found: 452.1210.
^{1}H NMR ($CDCl_3$), δ: 2.16 (3H, s, N^bCOCH_3); 2.55 (6H, s, $N^a(COCH_3)_2$); 4.18 (1H, dd, H-4); 4.85 (1H, d, H-2); 5.31(1H, broad at 297K, sharp dd at 323K, H-3); 6.08 (1H, d, H-5); 7.23 (2H, dm, C2-Ph *ortho* protons); 7.32 (2H, dm, C4-Ph *ortho* protons); 8.80 (1H, br, NH). [For compounds **4a-c** and **10**, 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].

Compound 4b. Prepared as **4a**. N-Ethyl-thiocinnamamide (500mg; 2.62mmol), pyridine (0.42ml; 5.24mmol) in acetone (5ml) was treated with acetyl chloride (0.37ml; 5.24mmol) in acetone (5ml) giving **4b** as a white crystalline solid after chromatography (SiO_2, 50% ethyl acetate/hexane) (213 mg; 38%), mp 157-158°C.
^{1}H NMR ($CDCl_3$), δ: 0.5 (3H, t, $N^bCH_2C\underline{H}_3$); 1.20 (3H, t, $N^aCH_2C\underline{H}_3$); 2.24 (3H, s, N^aCOCH_3); 2.88 (1H, m, $N^bC\underline{H}_xH_yCH_3$); 3.19 (1H, m, $N^bCH_x\underline{H}_yCH_3$); 3.53 (1H, m, $N^aC\underline{H}_xH_yCH_3$ and 3.68 (1H, m, $N^aCH_x\underline{H}_yCH_3$); 4.23 (1H, dd, H-3); 4.38 (1H, dd, H-4); 4.57 (1H, d, H-2); 5.74 (1H, bt, NH); 5.93 (1H, d, H-5); 7.28 (2H, dm, C4-Ph *ortho* protons); 7.33 (2H, dm, C2-Ph *ortho* protons).
Ms (m/e). 424[M]+, 334, 233, 191, 147, 77, 43. Analysis: calculated for $C_{24}H_{28}N_2OS_2$: C, 67.89%, H, 6.65%, N, 6.6%, S, 15.10%; found: C, 67.80%, H, 6.65%, N, 6.35%, S, 14.95%.

Compound 4c. This compound was isolated in 11% yield from the cycloaddition of N-ethyl-thiocinnamamide with cyclopentene (details will be given in a forthcoming paper).
Ms (m/e). 466[M]+, 233, 190, 147, 77, 43.
Accurate mass: calculated for $C_{24}H_{30}N_2O_2S_2$ 466.1748; found: 466.1741.
^{1}H NMR ($CDCl_3$), δ: 0.69 (3H, t, $N^bCH_2C\underline{H}_3$); 1.21 (3H, t, $N^aCH_2C\underline{H}_3$); 2.30 (3H, s, N^bCOCH_3); 2.40 (3H, s, N^aCOCH_3); 3.53 (1H, m, $N^bC\underline{H}_xH_yCH_3$); 3.59 (1H, m, $N^aC\underline{H}_xH_yCH_3$); 3.68 (1H, m,

$N^aCH_xH_yCH_3$); 4.08 (1H, m, $N^bCH_xH_yCH_3$); 4.39 (1H, dd, H-4); 4.75 (1H, dd, H-3); 4.91 (1H, d, H-2); 6.03 (1H, d, H-5); 7.14 (2H, dm, C4-Ph *ortho* protons); 7.20 (2H, dm, C2-Ph *ortho* protons).

Compound 10. A solution of **4a** (200mg; 0.44mmol) in deuteriochloroform (5ml) was heated at 65°C for 72h producing **10** in essentially quantitative yield. (A slower appearance of **10** was also seen using sodium-dried benzene in place of chloroform). Flash column chromatography (SiO_2; 30% ethyl acetate/hexane) gave the pure compound as a white solid (170mg; 85%), mp 77-79°C.
^1H NMR ($CDCl_3$), δ: 2.62 (6H, s, $N(COCH_3)_2$); 3.45 (1H, dd, C3-H); 3.85 (1H, dd, H-4); 4.63 (1H, d, H-2); 6.00 (1H, d, H-5); 7.31(2H, dm, C4-Ph *ortho* protons); 7.52 (2H, dm, C2-Ph *ortho* protons).
Ms (m/e). 376[M]+, 334, 293, 205, 161, 129, 103, 77, 57, 43. Accurate mass: calculated for $C_{22}H_{20}N_2O_2S$ 376.1245; found: 376.1235.

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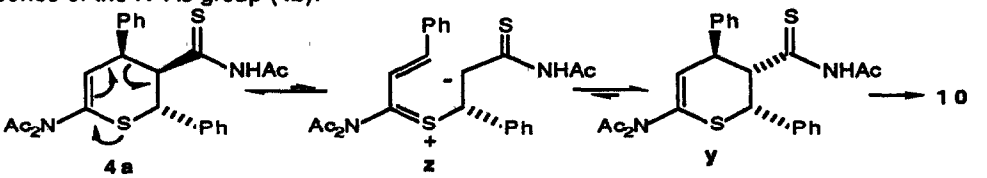
14. **4a(d) Was synthesized using a deuteriated precursor in an analogous fashion to that discussed for 4a. (Experimental details are available upon request).**
15. **During the 4a-->10 conversion process, followed in the NMR tube, a third compound was found to be present in some cases in varying but small amounts. At the completion of the 4a-->10 conversion, the compound had totally disappeared, and could not be isolated, nor could its structure be fully assigned. Nevertheless, the vicinal (H,H) couplings, together with the available NOE information, clearly identify it as diastereoisomer "III", again mainly in the "b" conformation** with some contribution from "a". [The NOE results (not included in Table 2), although limited due to signal overlaps, give analogous results to those found in **10**, clearly showing the short d(2;3), d(2;o-4) and d(4;o-2) distances]. {^{1}H NMR, δ: 2.07 (3H, s, $COCH_3$); 2.55 (6H, s, $N^a(COCH_3)_2$); 4.13 [1H, t (4.7 Hz), H-4]; 4.17 (1H, dd, H-3); 4.69 [1H, d (7.5 Hz), H-2]; 6.16 [1H, d (4.7 Hz), H-5]; 7.32 (2H, d, C4-Ph *ortho* protons); 7.40 (2H, d, C2-Ph *ortho* protons)}. The exact nature of the C-3 substituent is uncertain from the available NMR information; the compound is thus presumably either intermediate **x** or **y**.
16. An attractive alternative mechanism for epimerization at C-3 can be envisaged and involves cleavage of the C-4--C-3 bond to yield zwitterion **z**, which can ring close on either side of the C-3 anionic centre to yield either **4a** or **y**. However, since no β-nitrile isomer of **10** is ever observed during the reaction, it is not clear why the formation of only **y** would lead to nitrile according to this mechanism. Also, with this mechanism it is difficult to rationalize the complete lack of epimerization in the absence of the N^bAc group (**4b**).



17. It should be noted that these arguments imply that any measurable concentration of the "thiol-imide" tautomeric form in thioamides in general is known to be absent.[33] Similarly, there is no physical evidence for the existence of the "iminol" form in amides.[34] Thus, the N^bH proton can be regarded as being predominantly located on the nitrogen site in the CSNHAc moiety.
18. The comparison of these NOE intensities between **4a** and **4b** as being indicative of geometrical differences is justified by the fact that, from the point of view of the N^bH protons, H-2s are in very similar relaxational environments in both compounds. Although this intensity difference in the H-2--HN^b NOE interactions is also clearly reflected in the enhancements seen on the N^bH protons upon irradiating the H-2 signals, this allows for a less straightforward comparison due to the relaxationally somewhat different surroundings of the N^bH protons in **4a** and **4b**.
19. Weiner, S. J.; Kollman, P. A.; Case, D. A.; Singh, C.; Ghio, C.; Alagona, G.; Profeta, S.; Weiner, P. J. *J. Am. Chem. Soc.*, **1984**, *106*, 765.
20. The structures displayed in Fig. 2 are representations of the results of the MM calculations. The atomic coordinate data sets obtained directly from the MM calculations were transformed into the two-dimensional representations shown in the figure using the "ChemDraw®" program on a Macintosh SE personal computer, where the labelings were done. To improve clarity the Ph units were replaced by "Ph" labelings.
21. We wish to point out that here we are using the term "electrostatic interaction" rather than "hydrogen bonding" since in **4a**[1] generally accepted geometrical requirements for the formation of a "true" hydrogen bridge[35] are not strictly met.
22. In view of the inherent insensitivity of this experiment, the absence of an observed analogous heteronuclear NOE connection in **4a** is presumably (or at least partly) due to the fact that in that case the corresponding *anti* form is calculated to have less contribution in the isomeric equilibrium. Also, in terms of relaxation pathways, in **4a** the N^bHAc carbonyl is somewhat less isolated due to

the presence of the N^bH proton, which may diminish its ability to show the above enhancement. Furthermore, in the case of **4a**, the C=S carbon also proved to be unusually insensitive to showing an enhancement upon irradiating the H-3 signal. (It required a 72 hr experiment and carefully optimized conditions to give an unambiguous result but, even then, the achieved signal to noise ratio was about half that obtained in any other over-night $^{13}C\{^1H\}$ NOE experiments for **4a-c** and **10**). Although this insensitivity of the C=S carbon in **4a** is probably related to the relaxational characteristics of the C-3 substituent, the exact reason for it is not clear. It may well be, however, that this feature of the C-3 side chain is also connected to the lack of observed enhancement on the N^bAc carbonyl upon irradiating H-3.

23. H-2 And H-3 are strongly coupled in DMSO in **4c**, thus prohibiting meaningful NOE difference experiments in this solvent.
24. The "reverse" transferred effect was not observed on the C=S carbon upon the irradiation of H-2, probably because of relaxational reasons (see also ref. 22).
25. Note that the observed temperature and viscosity dependence of the intensity of the negative peaks is contrary to that normally expected for saturation transfer. The longer correlation times associated with higher solution viscosity (in our case in DMSO) or lower temperatures are, in the extreme narrowing region, related to more efficient T_1 relaxation which tends to work against saturation transfer. Thus, in our case relaxation influences alone would be expected to have the opposite effect in terms of the correlation time dependence of the size of the negative peaks to that observed. Furthermore, the non-selective T_1 relaxation times of all ring-protons in **4a** in $CDCl_3$ at room temperature were measured to be ca. 1s. This accords with the size and the expectedly nearly isotropic tumbling of the molecule. For completeness it is further noted that the possibility of a major contribution of scalar relaxation, which is known to give negative NOEs in specific cases,[36] and could be imagined to be brought about by the "labile" character of H-3 in **4a** and **4c**, can be ruled out on the basis that the J(2,3) couplings show no sign of the associated rapid modulation that would result in the collapse of the relevant multiplet patterns.
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28. One spectacular example underlining this point is seen in the -30°C NOE spectra of **4a** where H-3 (δ 5.50) is positioned closer to the H-5 (δ 6.10) than to the H-2 (δ 4.85) signal; while, as expected, no effect is seen on the H-5 signal upon irradiating H-3 (DP=55L), H-2 gives a -20% negative peak.
29. e.g. Sanders, J. K. M.; Mersh, J. D. *Progr. NMR Spectrosc.*, **1982**, *15*, 353 and references therein.
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34. e.g. Barton, D.; Ollis, W.D. in *Comprehensive Organic Chemistry*; (Sutherland, I.O. editor) vol 2, p 990. Pergamon Press, Oxford, **1979**.
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36. *a)* e.g. in Noggle, J. H.; Schirmer, R. E. *The Nuclear Overhauser Effect*; p 37. Academic Press, New York, **1971**. *b)* Fukumi, T.; Arata, Y.; Fujiwara, S. *J. Chem. Phys.*, **1968**, *49*, 4198.