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Formation and Mechanistic Implication of a Novel Thiaazabicyclooctane Derivative During the Cycloaddition of N-Acetyl Cinnamic Acid Thioamide

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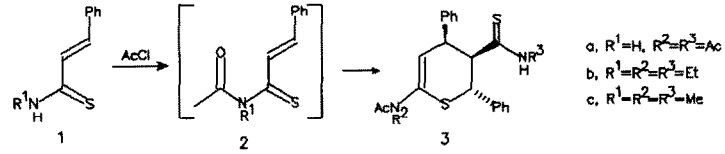
Key Words: 2-(N-Acylamino)-1-thia-1,3-dienes; cycloaddition; dihydrothiopyrans; thiaazabicyclooctane; NMR.

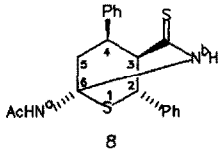
Abstract: *In the course of synthesizing thiopyran* **3a**, *the novel thiaazabicyclooctane derivative* **8**, *a precursor to* **3a**, *has been isolated as a major product. The formation of* **8** *provides further insight into the mechanism of the [4+ 2] cycloaddition involving* **1a**, *which we have previously discussed to be an efficient way of generating usefully functionalised dihydrothiopyrans. The structure of compound* **8** *was established by detailed NMR investigations.*

In preceding papers we reported[1,2] that 2-(N-Acylamino)-1-thia-1,3-dienes **2**, generated *in situ* from acylation of α,β - unsaturated thioamides **1**, undergo regiospecific and stereoselective Diels-Alder cycloaddition to a range of alkenes to yield usefully functionalised dihydrothiopyrans in good yields. In the absence of other dienophilic traps compounds **2a** and **2b** experience cycloaddition to the starting thioamides **1a,b** to give thiopyrans **3a,b**.[2a]



1 2 3

As we have discussed previously, a detailed NMR study of these compounds revealed unexpected negative peaks in the $^1H\{^1H\}$ NOE difference spectra of thiopyran **3a** (but not in **3b**) which, at present, seem to be inexplicable in terms of relaxation theory and cannot be linked to any conceivable chemical exchange process in **3a**.[2a] As a part of our continued interest in this problem, we reproduced thiopyrans **3a** and **3c**, the latter being the direct analogue of **3b**. Here we report that during this synthetic work we isolated the novel thiaazabicyclooctane derivative **8**, the formation of which provides further insight into the mechanism of the above cycloaddition process. In addition, this method affords a novel, rapid and efficient entry into the thiaazabicyclooctane system.[3]



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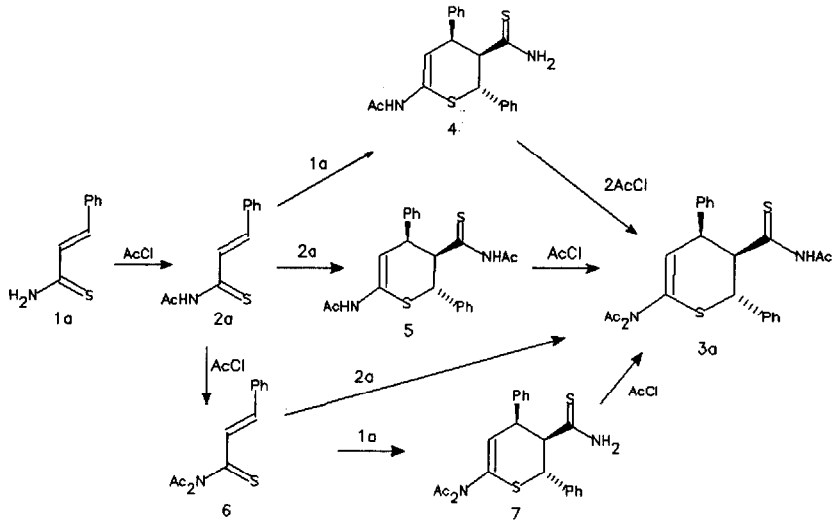
Thioamide **1a** (1.2 g = 7.5 mmol) was heated at reflux in a pyridine (1.1 ml) / acetone (22 ml) mixture in the presence of AcCl (1 ml = 15 mmol). After 3 hr, as monitored by TLC, **1a** had already disappeared and had converted mainly into **8**. Aqueous workup followed by chromatography of the resulting oil gave compound **8** (0.54 g) in 39% yield. (White crystals from EtOAc, mp 218-220°C). Further heating of **8** in the presence of excess AcCl afforded thiopyran **3a** in essentially quantitative yield.

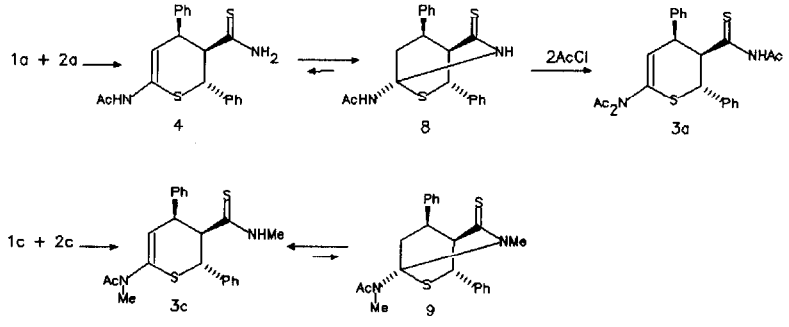
SCHEME 1



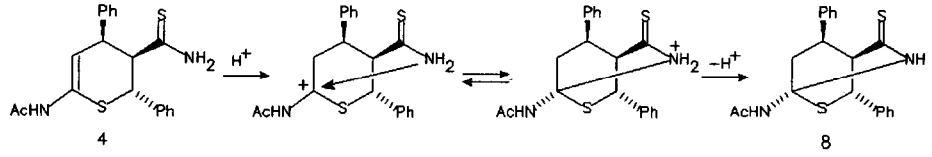
However, under similar reaction conditions **1c** gave rise directly to **3c**, and the intermediacy of a thiaazabicyclooctane derivative analogous to **8** (compound **9** in Scheme 2) was not observed.

Previously we have pointed out that formation of the final product **3a** may occur via several different pathways[2a] as shown in Scheme 1. Clearly, the formation of **8** must result from an intramolecular ring-closure in intermediate **4**; this finding provides direct experimental evidence that the main reaction route toward **3a** involves the [4+2] cycloaddition of **1a** and **2a**, while other pathways depicted in Scheme 1 have only minor contributions, if at all. This result is consistent with our FMO considerations[2] and adds to the understanding of the nature of this synthetically useful cycloaddition. While the **4** ⇌ **8** equilibrium is completely shifted toward the bridged structure **8**, the NMe compound **3c** exists predominantly in the "open" form, and no detectable amount of its thiaazabicyclooctane analogue **9** was observed (Scheme 2). We interpret this difference in the respective equilibria by structural considerations (see below).

SCHEME 2



A possible mechanism of the ring-closure in **4** is the following:

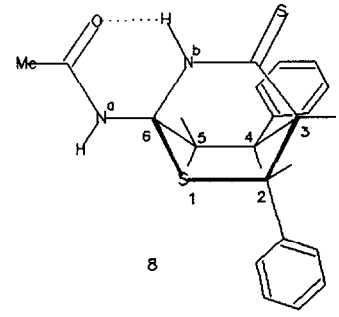


The constitution and stereostructure of compound **8** were unambiguously elucidated[4] by the use of high-field NMR methods, notably 1D $^1H\{^1H\}$ and selective $^{13}C\{^1H\}$ NOE difference experiments and 2D ^1H-^1H and ^{13}C-^1H shift correlated spectra. Characteristic ^1H chemical shifts and coupling constants are given in Table 1. The results of the $^1H\{^1H\}$ and $^{13}C\{^1H\}$ NOE experiments are listed in Table 2. Both the vicinal ^1H-^1H couplings and the NOE connectivities establish definitively the stereochemistry of compound **8** as shown in Figure 1 (for clarity unlabelled bonds denote H). For ^{13}C assignments see note 5. One notable feature of the homonuclear NOE results is that the proton transfer between the N^aH and N^bH protons has proved to be slow on the relaxation time-scale, thus resulting in no saturation transfer and transferred NOEs and allowing a straightorward interpretation of the observed enhancements. The strong downfield shift of the N^bH proton suggests that it is hydrogen bonded to the COMe oxygen. The $^1H\{^1H\}$ NOE results (in particular the strong COMe--HN^a but only very weak N^aH--HN^b dipolar interactions) are fully consistent with the prevalence of a coplanar conformation of the acetylamide side-chain which accommodates such a H bridge (Fig. 1). The presence of a very weak (<1%) N^aH--HN^b NOE connectivity, however, points to a small contribution of non H bonded rotameric forms of the C-6 side-chain in which these two protons are spatially close. All this is supported by the IR data.[6]

Table 1. Characteristic ^1H chemical shifts (δ_{TMS}=0.00 ppm) and J(H,H) coupling constants (Hz) for compounds **8** and **3c** ($CDCl_3$, 300 MHz). "o-2" and "o-4" refer to the C-2 Ph and C-4 Ph *ortho* protons, respectively.

	8			**3c** (M)		**3c** (m)	
proton	δ	J	proton	δ	J	δ	J
H-2	5.03		H-2	4.57		4.78	
H-3	3.70	2.2	H-3	4.29	11.7	4.12	3.6
H-4	3.51	1.4	H-4	4.38	4.6	3.63	4.9
		6.7 (4α,5β)	H-5	6.04	6.4	6.13	2.3
H-5β	2.58	10.6 (4α,5α)	N^bH	6.85		9.19	
H-5α	2.90	12.4	N^bMe	2.55	4.8	3.06	4.3
N^bH	10.06		N^aMe	3.17		3.37	
N^aH	6.30		COMe	2.27		2.27	
o-4	7.07						
o-2	7.61						
COMe	2.13						

FIG. 1



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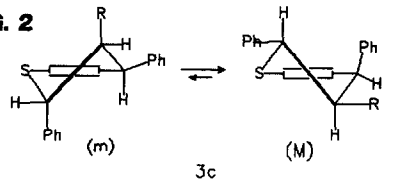
The NMe thiopyran **3c** gave ^1H and ^{13}C NMR data entirely analogous to those of its NEt derivative **3b**, the NMR parameters and stereochemistry of which were already analysed in detail.[2a] An interesting feature of **3c** is that besides the major (M) half-chair conformation of the thiopyran ring (Fig. 2), the concomitant half-chair isomer (m) is also present in about 15%. The rate of ring inversion is slow on the δ time-scale, giving rise to two sets of ^1H (see Table 1) and ^{13}C signals at 28°C. The existence of

Table 2. Results of the 1D $^1H\{^1H\}$ (in $CDCl_3$) and $^{13}C\{^1H\}$ (in DMSO) NOE difference experiments on compound **8**. The measured ^1H NOE intensities are denoted as "s" (strong, > 8%), "m" (medium, 3-8%), "w" (weak, 1-3%), "vw" (very weak, < 1%) and "n" (small negative enhancements due to three-spin effects). "o-2" and "o-4" refer to the C-2 Ph and C-4 Ph *ortho* protons, respectively.

	observed enhancements (^1H)										(quaternary ^{13}C)
Irr. H	H-2	H-3	H-4	H-5β	H-5α	N^bH	N^aH	COMe	o-4	o-2	
H-2	*	s	-	-	-	-	-	-	-	s	2-Ph *ipso* C
H-3	s	*	m	-	-	-	-	-	w	m	CS
H-4	-	m	*	n	s	-	-	-	s	m	
H-5β	-	-	n	*	s	-	w	-	s	-	
H-5α	-	-	m	s	*	-	m	-	n	vw	
N^bH	vw	-	-	vw	-	*	vw	-	vw	-	CS & C-6
N^aH	-	-	-	w	m	vw	*	s	-	-	CO & C-6
o-4	-	w	m	w	n	-	-	-	*	-	
o-2	m	w	w	-	-	-	-	-	-	*	

FIG. 2



3c

a dynamic equilibrium between the two ring invertomers was clearly demonstrated by the presence of strong saturation transfer effects connecting the analogous proton-pairs that are related by chemical exchange in the $^1H\{^1H\}$ NOE difference spectra of **3c**. The slowness of the ring interconversion is likely to be due to an expectedly strained transition state, with a strong steric repulsion between the C-3 side-chain and the C-4 Ph. The contribution of the (m) isomer in the NEt thiopyran **3b** is only about 1% probably because, as compared to **3c**, the more bulky C-3 side-chain entails larger steric effects in the (m) form.[7] In view of this we anticipate that in thiopyran **4**, which is a precursor to **8**, the (m) isomer is even more populated. Since the intramolecular ring-closure of **4** to give **8** can only proceed via the (m) form, the large contribution of such a conformer is expected to promote the ring-closing reaction.

As discussed above, the **4** ⇌ **8** and **3c** ⇌ **9** equilibria are shifted in the opposite sense, with **8** existing predominantly in the "bridged", while **3c** in the "open" form. We rationalize this difference by noting that the intramolecular $N^bH...O=C$ hydrogen bridge stabilizes the thiaazabicyclooctane system in the case of **8**; on the other hand the steric repulsion between the N^bMe and the $N^a(Me)COMe$ unit destabilizes compound **9** with respect to **3c**. As we have pointed out the conformation accommodating the $N^bH..O=C$ hydrogen bond in **8** is not exclusive. This fact, however, does not appreciably affect the free energy of the system.

REFERENCES AND NOTES

1. Barnish, I. T.; Fishwick, C. W. G.; Hill, D. R.; Szántay, Cs. Jr. *Tetrahedron Lett.*, **1989**, *30*, 4449.
2. a) Barnish, I. T.; Fishwick, C. W. G.; Hill, D. R.; Szántay, Cs. Jr. *Tetrahedron* **1989** *45*, 6771; b) *ibid.* 7879.
3. For previous examples of the generation of this ring-system see; a) Yamamoto, Y.; Ohnishi, S.; Morol, R.; Yoshida, *Chem.Pharm.Bull.*, **1983** *31*, 1936; b) Yamamoto, Y.; Ohnishi, S.; Morol, R.; Yoshida, A. *J. Chem. Soc. Chem.* Comm., **1983** 56; c) Reliquet, A.; Meslin, J. C.; Reliquet, F.; Sharrard, F.; *SulfurLett*, **1986** *5*, 97; d) Bakasse, M.; Duguay, G. *SulfurLett.*, **1990** *11*, 123.
4. In elucidating the structure of compound **8** we avoided any *apriori* assumptions on its stereochemistry. It is noted that the possibility of epimerization during or after the reaction may not be ruled out.[2a] In addition, we observed that thioamide **1a**, when left to stand in $CHCl_3$ at room temperature, slowly tends to equilibrate with its Z isomer, the possible participation of which in the Diels-Alder reaction may lead to various configurational isomers of the cycloadducts.
5. The assignments of the H-bearing and quaternary carbons of compound **8** were confirmed by 2D ^{13}C-^1H shift correlated and 1D $^{13}C\{^1H\}$ NOE experiments, respectively. Characteristic ^{13}C shifts (DMSO, $\delta_{DMSO\text{-}d6}$= 39.5 ppm), δ: 23.5 (COMe), 34.5 (C-4), 45.4 (C-5), 49.9 (C-2), 60.9 (C-3), 75.0 (C-6), 137.5 (2-Ph *ipso* carbon), 143.3 (4-Ph *ipso* carbon), 169.9 (COMe), 200.2 (CS).
6. Characteristic IR bands (cm^{-1}): 3200-2700 broad, m (H bonded NH); 3260 m (non H bonded NH); 3200 w (non H bonded NH, contribution from other rotameric forms); 1660 s (H bonded CO); 1690 m (contribution from non H bonded CO).
7. Any possible contribution of the (m) isomer in **3a** was undetectable which, in addition to the bulkiness of the side-chain, is likely to be a result of the attractive CS...H-3 dipol-dipol interaction present in the (M) form, as discussed in ref. 2a. It is further noted that this slow conformational motion in the NMe compound **3c** does not stem from a potentially hindered rotation of the C-3 thioamide side-chain. This is evident from the ^3J(H-2,H-3) couplings which show a pronounced difference in the two half-chair forms, and are consistent with the relevant dihedral angles (Table 1 and Fig. 2). In the case of the NEt cycloadduct **3b** (which is the direct analogue of **3c**) the conformational features of the C-3 side-chain *within* the (M) half-chair form were discussed before in detail.[2a]

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