Tetrahedron Letters,Vol.30,No.33,pp 4449-4452,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

GENERATION AND CYCLOADDITIONS OF 2-(N-ACYLAMINO)-1-THIA-1,3-DIENES

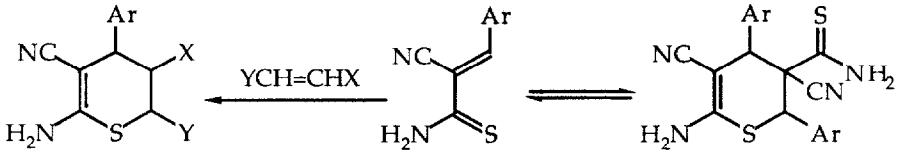
Ian T. Barnish,[b] Colin W.G. Fishwick,[a*] David R. Hill[a] and Csaba Szantay Jr.[a,1]

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

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

Summary: 2-(N-Acylamino)-1-thia-1,3-dienes are a new class of reactive hetero-1,3-diene which can be generated *in situ* via acylation of α,β-unsaturated thioamides. These systems undergo Diels-Alder cycloaddition with electron deficient, non-activated and electron rich alkenes to yield usefully functionalised dihydrothiopyrans.

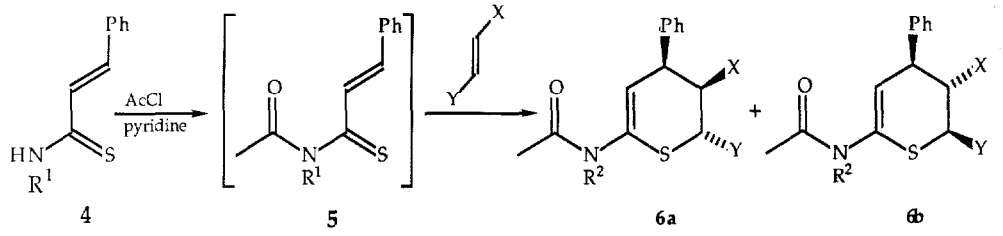
The Diels-Alder reaction is one of the most useful methods for the efficient construction of six-membered ring systems with a high degree of regio- and stereocontrol.[2] In addition, the hetero Diels-Alder reaction, in which the diene or dienophile contains one or more hetero atoms, has become established as a general method for the synthesis of six-membered heterocyclic ring systems.[3] There are several examples concerning the cycloaddition of systems containing the 1-thia-1,3-diene moiety; for instance, α,β-unsaturated thioaldehydes and ketones behave as reactive hetero dienes in Diels-Alder cycloadditions.[4] In contrast, the corresponding α,β-unsaturated thioamides are generally much less reactive, although it has been reported[5] that 3-aryl-2-cyanothioacrylamides (**1**) exist in equilibrium with the [4+2] dimers (**2**) and can also undergo intermolecular cycloaddition with electron deficient dienophiles yielding dihydrothiopyrans (**3**).[6]



3 **1** **2**

Scheme 1

We now report that the simpler α,β-unsaturated thioamides[7] (**4**, R^1 = H, Et), when acylated *in situ* in the presence of electron deficient, non-activated, or electron rich dienophiles produce usefully functionalised 6-(N-acylamino)-3,4-dihydro-2H--thiopyrans[8] (**6**, R^2 = COMe, Et) with regiospecificity and high stereoselectivity, presumably via the intermediacy of the N-acetyl thioamide (**5**) (Scheme 2). The results of similar cycloadditions are summarised in the Table.[9]



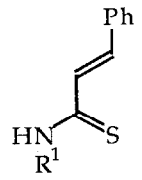
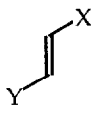
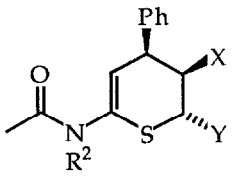
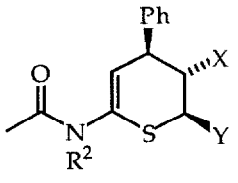
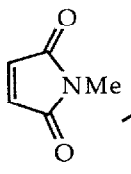
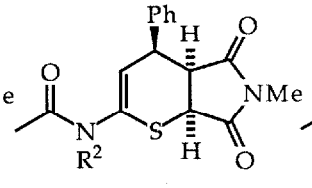
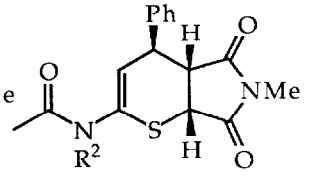
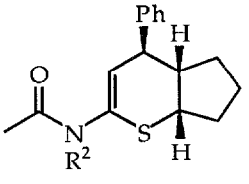
Scheme 2

Several points are noteworthy: (i) all cycloadditions are stereoselective and generally favour the formation of the endo-cycloadduct; (ii) cycloadditions with non-symmetrical dienophiles are regiospecific, the observed regiochemistry depending on the nature of the dienophile; (iii) N-acyl thioamides undergo cycloaddition to electron deficient (**7**, **8**, **9**, **11** and **12**), non-activated (**13** and **14**), and to electron rich (**10**) dienophiles.

In the absence of acetyl chloride the thioamides themselves are completely unreactive towards dienophiles, and are recovered in full even after prolonged heating with a dienophilic trap. In addition, the starting thioamides (**4**) showed no tendency to undergo [4+2] dimerisation, in contrast to the behaviour of the related α-cyano system (**1**).[5] In the absence of added dienophiles, adducts (e.g. **6a**, R^2=Et, X=CSNHEt, Y=Ph) arising via an initial [4+2] cycloaddition of the N-acyl thioamides (**5**) to the starting thioamides (**4**) are obtained in moderate yields as stable crystalline solids.

The regio- and stereochemistry of the cycloadditions described herein appear to be in complete accordance with frontier molecular orbital symmetry predictions.[10] Studies concerning the synthetic scope of these cycloadditions are now in progress.

Table. [4+2] Cycloadditions of N-acyl thioamides (5).

Thioamide (4)	Dienophile	Products		Yield (%)[a]
				
R^1 = H	X = Y = CO_2Me	**7a** R^2 = COMe X = Y = CO_2Me	**7b** R^2 = COMe X = Y = CO_2Me	15[b](4:1)
		7c R^2 = H X = Y = CO_2Me	**7d** R^2 = H X = Y = CO_2Me	30 (4:1)
R^1 = Et	X = Y = CO_2Me	**8a** R^2 = Et X = Y = CO_2Me	**8b** R^2 = Et X = Y = CO_2Me	81 (7:1)
R^1 = Et	X = CN, Y = H	**9** R^2 = Et X = CN, Y = H		38
R^1 = Et	X = H, Y = OEt	**10a** R^2 = Et X = H, Y = OEt	**10b** R^2 = Et X = H, Y = OEt	30 (1:4)
				
R^1 = Et		**11a** R^2 = Et	**11b** R^2 = Et	60 (4:1)
R^1 = H		**12a** R^2 = COMe	**12b** R^2 = COMe	21[b](2:1)
				
R^1 = Et		**13** R^2 = Et		86
R^1 = H		**14** R^2 = COMe		47[b]

Notes :

(a) The ratio of isomers is given in parentheses. All new compounds gave IR, NMR and mass spectral data which were consistent with the proposed structures.

(b) In addition, a substantial amount of cinnamonitrile was isolated.

Acknowledgments : We should like to thank the SERC and Pfizer Central Research for a CASE award to DRH.

References and notes

1. On leave from the NMR laboratory of the Institute for General and Analytical Chemistry, Technical University, H-1521 Budapest, Hungary.
2. Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 779.
3. Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, New York, **1987**.
4. Lipkowitz, K. B.; Mundy, B. P. *Tetrahedron Lett.*, **1977**, 3417; Karakasa, T.; Motoki, S. *J. Org. Chem.*, **1978**, *43*, 4147 ; *ibid*, **1979**, *44*, 4151 ; *ibid*, **1980**, *45*, 927.
5. Brunskill, J. S. A.; De, A.; Ewing, D. F. *J. Chem. Soc., Perkin Trans. I*, **1978**, 629; *J. Chem. Soc., Perkin Trans. II*, **1980**, 4.
6. El-Sharabasy, S. A.; Hussain, S. M.; Abdel Gawad, S. M.; Daboun, H. A. *Indian J. Chem.*, **1988**, *27B*, 472.
7. Prepared by the reaction of the corresponding amides with P_2S_5, according to the method of Pravdic, N. ; Hahn, V. *Croatica Chemica Acta*, **1962**, *34*, 85. Chem. Abs., **1962**, *57*, 12377.
8. In a typical experiment, N-ethyl thiocinnamamide (2.0g ; 10.5mmol), (**4**, R^1 = Et) was dissolved in pyridine (1.7ml ; 21.0mmol) and acetone (20ml) containing dimethyl fumarate (1.7g ; 11.5mmol) and this solution was then heated to 65°C. Acetyl chloride (1.5ml ; 21.0mmol) in acetone (20ml) was then added dropwise and the resulting red solution was maintained at 65°C for a further 18 h. After cooling and aqueous work-up, chromatography (SiO_2, 50% ethyl acetate / hexane) yielded 3.28g (83%) of an isomeric mixture of cycloadducts (**8a** and **8b**, Table) as a pale yellow solid. The cycloadducts were separated by fractional crystallisation from ether to give **8a** (2.56g ; 71%) and **8b** (0.36g ; 10%).
9. The structures of all cycloadducts were determined using a combination of high field NMR techniques. Representative data are shown below.[10]

8a ^{1}H NMR ($CDCl_3$), d: 1.10 (3H, t, -$CH_2\underline{CH_3}$); 2.15 (3H, s, $COCH_3$); 3.31 (1H, dd, H-3); 3.48 (3H, s, OCH_3); 3.43-3.65 (2H, m, -$\underline{CH_2}CH_3$); 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).

8b ^{1}H NMR ($CDCl_3$), d: 1.10 (3H, t, -$CH_2\underline{CH_3}$); 2.14 (3H, s, $COCH_3$); 3.16 (1H, t, H-3); 3.39 (3H, s, OCH_3); 3.43-3.65 (2H, m, -$\underline{CH_2}CH_3$); 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).

10. Full details will be published elsewhere.

(Received in UK 21 June 1989)