Tetrahedron Vol. 38, No. 11, pp. 1673 to 1676, 1982
Printed in Great Britain.

0040-4020/82/111673-04$03.00/0

SYNTHESIS OF 1,1-DIAMINO-2-THIOACYLETHYLENES: A NOVEL *C*-THIOACYLATION BY THE WILLGERODT-KINDLER REACTION†

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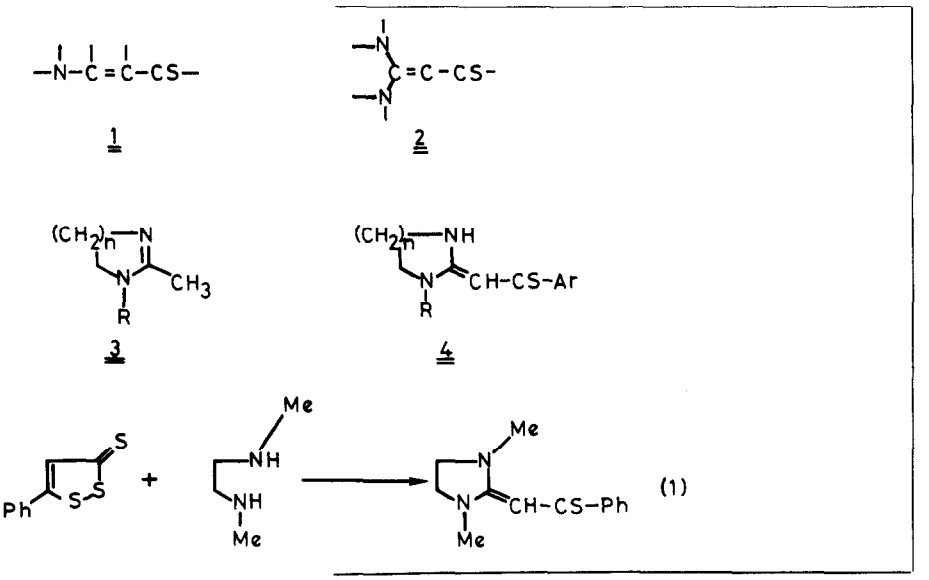
(*Received in U.K. 5 March* 1981)

Abstract—A novel *C*-thioacylation reaction is described. Reaction of aromatic or heterocyclic aldehydes with 1-alkyl-2-methyl-1,4,5,6-tetrahydropyrimidine or 1-alkyl-2-methylimidazolidine in the presence of sulphur leads to the thioacylketeneaminals **6**, **10** or **12** in low to moderate yields. The structure of **6e** was proved by *S*-methylation to **7e** and acid-hydrolysis to the known **8e**. Oxidative cyclization of **6** leads to the isothiazolo[2,3-*a*] pyrimidinium salts **13**.

1-Amino-2-thioacylethylenes (enaminothioketones) (**1**) are well-documented structural entities.[1] They are normally prepared from the corresponding enaminoketones, or from vinylogous iminium chlorides. In contrast, 1,1-diamino-2-thioacylethylenes (thioacylketeneaminals) (**2**) appear to be rarities in the literature; the only report[2] of the synthesis of such a thioacylketeneaminal proceeds as shown in eqn (1). The present paper deals with the synthesis of thioacylketeneaminals by a novel *C*-thioacylation reaction; in addition, some chemical transformations of these novel substituted enamines are also reported.

In order to achieve this projected thioacylation, we considered several thioacylating agents initially. Although thiobenzoyl chloride itself can be prepared in reasonable yields, other aromatic thioacid chlorides are obtained in very poor yields; they are also rather unstable.[4] Carboxymethyl dithiobenzoate is a good thioacylating agent for amines.[5] However it failed to react with 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (**5**). In the Willgerodt–Kindler reaction, amines are thioacylated by a combination of an aldehyde and elemental sulphur.[6] It seemed an intriguing possiblity, therefore, to achieve the required *C*-thioacylation of **3** by reaction



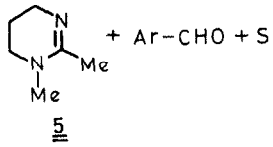
Our objective was to synthesise cyclic thioacylketeneaminals (**4**). We decided to investigate the possibility of making them by thioacylating the cyclic amidines (**3**). This follows from our earlier success in acylating such amidines by means of acid chlorides to give acylketeneaminals.[3]

with aromatic aldehydes in the presence of sulphur.

Reaction of amidine (**5**) with benzaldehyde and sulphur in refluxing xylene gave a product $C_{13}H_{16}N_2S$, whose mass spectrum showed the M^+ peak at 232 (100%). Its ^1H NMR spectrum agreed with structure **6a**. Similar reaction of **5** with thiophene 2-aldehyde and sulphur gave **6e**. The general reaction can be represented as in eqn (2). The structure of **6e** was confirmed as follows: *S*-Methylation of **6e** with methyl iodide, followed by mild

†Contribution No. 606 from Ciba-Geigy Research Centre.

acid-hydrolysis gave **8e**, identical with the product described earlier.[3]



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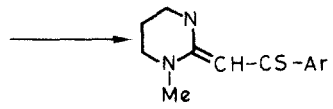

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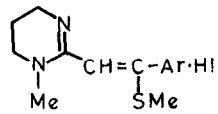

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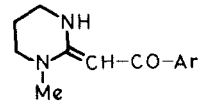

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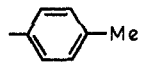
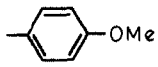
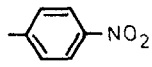
a: 

b: 

c: 

d: 

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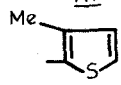
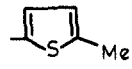
f: 

g: 

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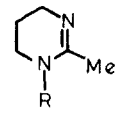
Scope and limitations of the reaction

(a) *Aldehyde component.* Various aromatic and heterocyclic aldehydes have been used in the reaction leading to products in low to moderate yields (Table 1). Only one attempt was made to use an aliphatic aldehyde; no characterisable product was obtained when pivalaldehyde was reacted with the amidine (**5**) and sulphur.

(b) *The amidine component.* Apart from **5**, the cyclic amidines **9(a, b)**[7] and **11a**[8] have been successfully used as substrates in the reaction with thiophene 2-aldehyde and sulphur; the yields of the products **10(a, b)** and **12** are listed in Table 1. Apparently it is necessary to have an *N*-alkyl substituent in the amidine, since **11b** gave only resinous material in the reaction.



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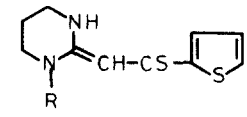
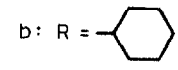
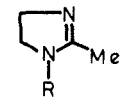


10

a: R = Et

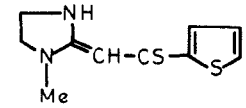
b: R = 



11

a : R = Me

b : R = H



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Further transformations of thioacylketeneaminals

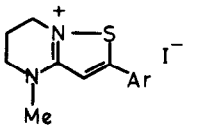
(a) *S-Alkylation.* Methyl iodide reacts easily with these compounds to produce the *S*-methyl derivatives **7**, isolated as their hydriodides. We describe in the

Table 1. Product yield in the thioacylation reaction

Compound	Yield %	Compound	Yield %
6a	23	10a	35
6b	16.2	10b	26
6c	15.2	12	33.5
6d	5.4		
6e	36.8		
6f	37.8		
6g	24.4		
6h	9		
6i	6.8		

experimental section, the products **7a**, **7e** and **7f** derived respectively from **6a**, **6e** and **6f**. The chemical shifts of the methyl groups and the methine proton in these three compounds, determined in $CDCl_3$ solution, are shown in Table 2.

(b) *Oxidative* S–N *bond formation.* Oxidation of **6** with sulphuryl chloride leads to the closure of the isothiazolium ring. The products **13a** and **13e** from **6a** and **6e** could be characterised as their crystalline iodides.



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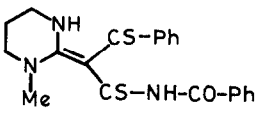

14

a : Ar = Ph

e : Ar = 

(c) *Reaction with isothiocyanates.* **6a** did not react with phenyl isothiocyanate in refluxing toluene, indicating its weaker enaminic reactivity compared to the acylketeneaminal **8a**. With benzoyl isothiocyanate, it easily formed the adduct **14**.

Chemical shift of the enaminic proton

The chemical shift of the enaminic methine proton in pairs of structurally similar enaminoketones and enaminothioketones have been compared before.[9] There is a significant downfield shift in the thio compounds as compared to the oxo compounds. This $\Delta\delta$ is of the order of 0.9 ppm. The downfield shift is even more pronounced when one compares the thioacylketeneaminals (**6**) with the corresponding oxo compounds (**8**) (Table 3).

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian A-60 instrument; chemical shifts are expressed in δ values (ppm) downfield from TMS.

A. *General procedure for the thioacylation*

A mixture of the amidine (0.02 mol), aldehyde (0.02 mol) and sulphur (0.025 to 0.03 mol) was stirred and refluxed in xylene (100 ml) under nitrogen for 5–8 hr. After cooling, the xylene was decanted off. The decantate was extracted with 2N HCl and the acid solution cooled and basified. The liberated product was extracted in ethyl acetate or CH_2Cl_2, chromatographed over alumina in $CHCl_3$ solution, evaporated and crystallized from a suitable solvent. The xylene—insoluble residue from the reaction was separately extracted in CH_2Cl_2, evaporated, and chromatographed over alumina in $CHCl_3$ solution. A small quantity of the required product was sometimes obtained in this eluate also.

1-*Methyl-2-(thiobenzoyl methylene)hexahydropyrimidine* (**6a**), m.p. 133–136° (from ethyl acetate). (Found: C, 67.40; H, 7.10; N, 11.74. $C_{13}H_{16}N_2S$ requires C, 67.22; H, 6.94; N, 12.06%). NMR ($CDCl_3$): 6.30 (CH).

1-*Methyl-2-(thio-*p*-toluoyl methylene)hexahydropyrimidine* (**6b**), m.p. 142–144° (from ethyl acetate). (Found: C, 68.00; H, 7.39; N, 11.43. $C_{14}H_{18}N_2S$ requires C, 68.27; H, 7.37; N, 11.37%). NMR ($CDCl_3$): 6.30 (CH).

1-*Methyl-2-(4-methoxythiobenzoyl methylene)hexahydropyrimidine* (**6c**), m.p. 134–136° (from ethyl acetate). (Found: C, 64.10; H, 7.15; N, 10.82. $C_{14}H_{18}N_2OS$ requires C, 64.10; H, 6.92; N, 10.68%). NMR ($CDCl_3$): 6.37 (CH).

1-*Methyl-2-(4-nitrothiobenzoyl methylene)hexahydropyrimidine* (**6d**), m.p. 200–203° (from ethyl acetate). (Found: C, 56.50; H, 5.68; N, 15.26. $C_{13}H_{15}N_3O_2S$ requires C, 56.31; H, 5.45; N, 15.16%). NMR ($CDCl_3$): 6.37 (CH).

1-*Methyl-2-(thio-2-thenoyl methylene)hexahydropyrimidine* (**6e**), m.p. 161–164° (from ethyl acetate). (Found: C, 55.71; H, 6.19; N, 11.65. $C_{11}H_{14}N_2S_2$ requires C, 55.45; H, 5.92; N, 11.76%). NMR ($CDCl_3$): 6.50 (CH).

1-*Methyl-2-[(3-methyl)thio-2-thenoyl methylene]hexahydropyrimidine* (**6f**), m.p. 117–120° (from ethyl acetate). (Found: C, 57.45; H, 6.70; N, 10.81. $C_{12}H_{16}N_2S_2$ requires C, 57.13; H, 6.39; N, 11.11%). NMR ($CDCl_3$): 6.25 (CH).

Table 2. ^{1}H NMR data for the hydriodides **7**

Compound	δSMe	δNMe	δCH
7a	2.12	3.30	6.28
7e	2.37	3.30	6.50
7f	2.22	3.12	6.10

Table 3. Chemical shift (ppm) of the enaminic proton in thioacylketeneaminals **6** and acylketenaminals **8**

δ_{CH} in **6**		δ_{CH} in **8**	
Compound	δ	Compound	δ
6a	6.30	**8a**	5.23
6d	6.37	**8d**	5.30
6e	6.50	**8e**	5.20

All except **8d** in $CDCl_3$; **8d** in DMSO-d_6 + $CDCl_3$

1-*Methyl*-2-[(5-*methyl*)*thio*-2-*thenoyl methylene*]*hexahydropyrimidine* (**6g**), m.p. 155–158° (from methanol). (Found: C, 57.48; H, 6.61; N, 10.98. $C_{12}H_{16}N_2S_2$ requires C, 57.13; H, 6.39; N, 11.11%). NMR ($CDCl_3$): 6.32 (CH).

1-*Methyl*-2-(*thio*-2-*furoyl methylene*)*hexahydropyrimidine* (**6h**), m.p. 144–147° (from ethyl acetate). (Found: C, 59.55; H, 6.46; N, 12.29. $C_{11}H_{14}N_2OS$ requires C, 59.45; H, 6.35; N, 12.60%).

1-*Methyl*-2-(*pyrrole*-2-*carbonothioyl methylene*)*hexahydropyrimidine* (**6i**), m.p. 164–166° (from ethyl acetate–hexane). (Found: C, 59.86; H, 7.17; N, 19.17. $C_{11}H_{15}N_3S$ requires C, 59.71; H, 6.83; N, 18.99%). NMR ($CDCl_3$): 6.47 (CH).

1-*Ethyl*-2-(*thio*-2-*thenoyl methylene*)*hexahydropyrimidine* (**10a**), m.p. 155–157° (from ethyl acetate). (Found: C, 57.72; H, 6.78; N, 10.92. $C_{12}H_{16}N_2S_2$ requires C, 57.13; H, 6.39; N, 11.11%). NMR ($CDCl_3$): 6.43 (CH).

1-*Cyclohexyl*-2-(*thio*-2-*thenoyl methylene*)*hexahydropyrimidine* (**10b**), m.p. 179–183° (from ethyl acetate). (Found: C, 62.67; H, 7.53; N, 8.85. $C_{16}H_{22}N_2S_2$ requires C, 62.72; H, 7.24; N, 9.14%). NMR ($CDCl_3$): 6.60 (CH).

1-*Methyl*-2-(*thio*-2-*thenoyl methylene*)*imidazolidine* (**12**), mp. 200–202° (from CH_2Cl_2–hexane). (Found: C, 53.73; H, 5.67; N, 12.38. $C_{10}H_{12}N_2S_2$ requires C, 53.57; H, 5.39; N, 12.50%). NMR (DMSO-d_6): 6.50 (CH).

B. *General procedure for the methylation of the thioacylketeneaminals* (**6**)

The thioacylketeneaminal **6** (1.0 g) in methanol (80 ml) was refluxed with methyl iodide (3.0 g) for 2 hr, the solvent removed in vacuo and the product crystallized.

1 - *Phenyl* - 1 - *methylthio* - 2 - (1 - *methyl* - 1,4,5,6 - *tetrahydro* - 2 - *pyrimidinyl*) *ethylene hydriodide* (**7a**), yield 1.3 g, m.p. 162–166° (from isopropanol). (Found: C, 45.13; H, 5.31; N, 7.16. $C_{14}H_{18}N_2S$. HI requires C, 44.93; H, 5.12; N, 7.49%).

1-*Methylthio* - 1 - (2 - *thienyl*) - 2 - (1 - *methyl* - 1,4,5,6 - *tetrahydro* - 2 - *pyrimidinyl*)*ethylene hydriodide* (**7e**), yield 1.5 g, m.p. 127–130° (from isopropanol–ether). (Found: C, 38.19; H, 4.66; N, 7.02. $C_{12}H_{16}N_2S_2$. HI requires C, 37.91; H, 4.51; N, 7.37%).

1 - *Methylthio* - 1 - (3 - *methyl* - 2 - *thienyl*) - 2 - (1 - *methyl* - 1,4,5,6 - *tetrahydro* - 2 - *pyrimidinyl*)*ethylene hydriodide* (**7f**), yield 1.3 g, m.p. 188–189° (from isopropanol–methanol). (Found: C, 40.13; H, 5.23; N, 6.95. $C_{13}H_{18}N_2S_2$. HI requires C, 39.60; H, 4.86; N, 7.11%).

C. *Hydrolysis of* **7e** *to* **8e**

The hydriodide **7e** (0.5 g) was warmed with 2N HCl (5 ml) to get a clear solution and left at 30° for 15 hr. It was then basified with 2N NaOH, extracted with ethyl acetate, dried and evaporated. The residual oil was passed through a short column of alumina in $CHCl_3$, evaporated and crystallized from ethyl acetate-hexane to give **8e** (0.1 g), m.p. and mixed m.p. with an authentic sample,[3] 126–128°.

D. *Oxidative cyclization of thioacylketeneaminals to isothiazolo*[2,3-a] *pyrimidinum salts* (**13**)

2-*Phenyl*-4-*methyl*-4,5,6,7-*tetrahydro isothiazolo*[2, 3-a] *pyrimidinium iodide* (**13a**). Sulphuryl chloride (1 g) was added dropwise to a cooled, stirred solution of **6a** (2 g) in CH_2Cl_2 (100 ml). After 30 min, ether was added to precipitate the product, the solvent decanted off and the residue dissolved in water and filtered. The filtrate was treated with a solution of potassium iodide (1 g in 25 ml water), cooled, and the solid filtered and washed with water to give the *iodide* **13a** (1.3 g), m.p. 238–241° (dried at 30° in vac). (Found: C, 43.63; H, 4.48; N, 8.26. $C_{13}H_{15}IN_2S$ requires C, 43.59; H, 4.22; N, 7.82%). In the NMR spectrum, (DMSO-d_6), the CH signal had moved downfield and merged with Ar-H at 7.6–8.1 ppm.

2-(2-*Thienyl*)-4-*methyl*-4,5,6,7-*tetrahydro isothiazolo*[2,3-a] *pyrimidinium iodide* (**13e**). Oxidative cyclization of **6e** (2.3 g) in $CHCl_3$ (50 ml) with sulphuryl chloride (1.4 g) at 10°, and isolation of the product as the iodide as above, gave **13e** (0.95 g), m.p. 180–185°. (Found: C, 36.70; H, 3.89; N, 7.63. $C_{11}H_{13}IN_2S_2$ requires C, 36.28; H, 3.60; N, 7.69%).

E. 1-*Methyl*-2-(α-*thiobenzoyl*-α-*benzamido thiocarbonyl*)*methylene*-1,4,5,6-*tetrahydropyrimidine* (**14**)

A soln of **6a** (1.1 g) in acetonitrile (20 ml) was treated with benzoyl isothiocyanate (0.8 g) and left at 30° for 3 hr. Ether was then added to the solution, the solid filtered and washed with ether to give the adduct **14** (1.5 g) as colourless crystals, m.p. 130–133°. (Found: C, 63.51; H, 5.59; N, 10.95. $C_{21}H_{21}N_3OS_2$ requires C, 63.79; H, 5.35; N, 10.63%).

Acknowledgement—We thank Dr. S. Selvavinayakam and his associates for the analytical and spectral data.

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