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## PREPARATION AND ALKYLATION OF CYCLIC AND NON-CYCLIC ENAMINO-THIONES

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Abstract—Enamino-thiones of the general type  $ArC(S)CH:CHNR_2$ , 3 (Ar = phenyl, p-methoxyphenyl and p-bromophenyl,  $NR_2 = pyrrolidinyl, piperidino), were prepared by reacting the corresponding enaminones, 2. with 2,4-bis-(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 1. The compounds 3 were reacted with methyl iodide and ethyl iodide to give exclusively S-alkylated iminium iodides, 4 and 5, in quantitative overall yields. N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinethione, 8, and 2-methyl-N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinethione, 8, and 2-methyl-N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinethione, 9, were alkylated with methyl iodide, ethyl iodide and benzyl bromide giving S-alkylated hexahydro-quinolinium halides, 10 and 11, respectively, in high yields. The stereochemistry of the compounds of types 4 and 5 is discussed in detail.$ 

Although enamino-thiones have been known for some time, the chemistry of this class of compounds<sup>2-10</sup> has received little study. Enamino-thiones of the general type  $ArC^{1}(S)C^{2}H:C^{3}HNR_{2}$  have, *a priori*, nucleophilic centres<sup>2-3</sup> at the S-, C(2)- and N-atoms, but experimentally only the nucleophilic properties at the S-atom have been described. Further, enamino-thiones possess two sites for a nucleophilic attack<sup>4-6</sup> at the C(1)- and C(3)-atoms.

Quiniou et  $al.^2$  have investigated the reaction between methyl iodide and secondary and tertiary enamino-thiones, but no spectroscopic details have been given. As part of general studies in this field we felt prompted to investigate alkylation of anamino-thiones as well as studying the stereochemistry of the products 4 and 5.

In a recent paper<sup>1</sup> we presented a new procedure for the preparation of enamino-thiones in high yields from the corresponding enaminones. Some improvements are described here.

#### **RESULTS AND DISCUSSION**

The preparation of enamino-thiones has been improved greatly<sup>1,11</sup> by reacting the thiation reagent 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiad1phosphetane-2,4-disulfide, 1,<sup>12</sup> with the corresponding enaminones, **2**.

The reaction takes place at room temperature or lower and the yields are high (Table 1). It should be emphasized that it is of crucial importance to separate the enaminothione from the unknown phosphorouscontaining products before recrystallization, since otherwise only polymers and by-products are obtained.

The compounds 3 are known to show restricted rotation around the C(1)-C(2) and C(3)-NR<sub>2</sub> bonds, due to delocalization of the free electron pair on nitrogen,  $^{13-15}$  and exist as two rotameric conformers, 3' and 3''.<sup>20</sup>

This equilibrium shows dependence on the C(1) substituent, and with bulky ones 3' is dominant. The compounds 3 were reacted with methyl iodide and ethyl iodide in acetonitrile giving the corresponding S-alkylated iminium iodides, 4 and 5, in quantitative overall yields. The proof of S-alkylation was given by off-resonance  ${}^{13}$ C NMR spectroscopy (e.g. 4f/5f, Table 3). According to the above discussion it is expected that two isomers will result. This is also found and the *E*-isomer, 5, is proved to be dominating (Table 2).

The ratio of 4 to 5 can be found by <sup>1</sup>H NMR analysis since there is a shift difference between  $-S-CH_2-R$  of the compounds 4 and 5 with the former conformer resonating at higher field.





<sup>+</sup>Part XVIII. S. Carlsson and S.-O. Lawesson, *Tetrahedron* 36, 3585 (1980).

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The structural proofs are made in two ways: By comparison with shift values of enamino-thiones at low temperatures, where both *E-s-E* and *E-s-Z* rotamers can be identified and by hydrolysis of the iminium iodide.

It is known<sup>14–16</sup> that H(3) resonates at  $\delta > 8.2$  ppm for the *E*-s-*Z* rotamer while for the *E*-s-*E* rotamer this resonance is at  $\delta < 8$  ppm. The compounds **4** and **5**  show a resonance at  $\delta = 8.0$  ppm while the resonance at  $\delta > 8$  ppm was broadened and of low intensity (except for the compounds **4f** and **5f**). This indicates compound **5** to be the main product, since according to the above discussion this rotamer is expected to show a resonance at  $\delta \le 8$  ppm. Additional evidence is given by the hydrolysis of **4a** + **5a** giving







5

Enamino- thione 3	Alkyl iodide R-I	Overall yield (%)	Iminium 4 (%)	iodide 5 (%)	mp./°: 4&5
	сн, і	96	5	95	168
ð	_	88	10	90	186
c	-	92	10	90	210
¢	-	91	8	92	200
	-	92	18	82	184
f	-	93	28	72	188
e	CH3 CH2 I	93			115 <sup>b)</sup>
h	-	89			175
1	-	89	( <sub>&lt; 5</sub> a)	>o'₅a)	184 、
j	-	88	$\left( \right) \right)$		146 <sup>b)</sup>
k	-	88			190
1	-	94	JJ		150 <sup>ь)</sup>

a) 4 was observed in all spectra, percentage uncertain.

b) Decomposition.

Z(6a)- and E(7a)-3-methylthio-3-phenylpropenal<sup>2</sup> in 60% overall yield. The H(2) resonances of 6a and 7a have been calculated<sup>19</sup> and compared with observed values: 6a (<5%), (calc.  $\delta = 6.58$ , observed  $\delta = 7.2$ (d, J = 7.2 Hz)), 7a (>95%), (calc.  $\delta = 5.99$ , observed  $\delta = 6.04$  (d, J = 8.0 Hz)). The compound 7a corresponds to 5a showing this compound as the main one. The structures of the products 4b-41/5b-51 have been determined by comparison with 4a/5a proving the compound 5 to be the main product. Expecially 4f/5f is interesting since 4f is formed in 28% yield making it possible to assign all resonances in <sup>1</sup>H NMR and <sup>12</sup>C NMR for both compounds (Table 3).

It is noted that in both 4f and 5f the C(1) carbons resonate at the same frequency. This indicates lack of delocalization of the positive charge in both isomers. Further the different shifts of C(2) and C(3) carbons of the two isomers support this interpretation, since the latter effect can be ascribed totally to the Z,E isomer effect. Also N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinthione, **8**, and 2-methyl-N-phenyl-2,3,5,6,7,8-hexahydro-4-quinolinethione, **9**, were reacted with methyl iodide, ethyl iodide and benzyl bromide giving Salkylated hexahydro-quinolinium halides in high yields (Table 4).

#### **EXPERIMENTAL**

<sup>1</sup>H NMR spectra were recorded at 60 MHz on a Varian A-60 or a Varian EM-360 spectrometer. <sup>13</sup>C NMR spectra were recorded at 20 MHz on a Varian CFT-20 spectrometer. TMS was used as internal standard and chemical shifts are expressed in  $\delta$ -values. CDCl<sub>3</sub> was used as a solvent. IRspectra were recorded on a Beckman IR 18A spectrometer. Mass spectra were recorded on a Micromass 7070 Mass spectrometer operating at 70 eV using direct inlet. Elementary analyses were carried out by Novo Microanalytical Laboratory, Novo Industry A/S. Novo Allé, DK-2880 Bagsværd, supervised by Dr. R. E. Amsler. M.ps are uncorrected.





4 f



5f

		<sup>1</sup> H NMR	12C NMR <sup>b,c)</sup>		
a55	<b>4</b> £	5 £	4 E	<b>5</b> f	
c <sub>1</sub>	9.03(J=11)	tz) 7.65(J=11 Hz)	159.32(d)	159.82(0)	
C,	6.90(J=11 1	iz) 6.73(J=11 Hz)	116.99(J)	109.91(d)	
c,		. \	174.98(s)	179.29(s)	
S- <u>С</u> Н3	2,29	2,86 <sup>d</sup>	18.05(q)	18.84(q)	
Р			127.00(s)	126.52(3)	
0	]a)	3-1-0	٦ 131.18	131,18	
м	}7.4-7.8	] 7.4-7.8	$J_{132.52}^{(a)}$	132.52	
s			134.93(s)	133.04(s)	
<u> </u>	4.2	14.2	r 60.47 (a)	100.47 (.)	
01	l3.9	(3.9	1 52.71	152.09	
C2 1	J	J	$\binom{26,66}{26,11}(t)$	$\binom{26.66}{26.11}(t)$	
C <sub>3</sub> '	}1.9	\$1.9	22.75(t)	22.75(t)	

a) A<sub>2</sub>B<sub>2</sub> spin system.

b) Assignment made by comparison with  $^{13}$ C NMR spectrum of 4a/5a using the relative intensities to distinguish between 4f and 5f.

c) Off-resonance <sup>13</sup>C NMR spectrum gives the multiplicities of the carbon resonances (s = singlet, d = doublet, t = triplet, q = quartet.

d Saturation of the S-CH<sub>3</sub> protons at t = 2.86 ppm gives a positive NOE for the H<sub>2</sub> proton at t = 6.73 ppm.

The enaminones 2a, d, f are known,<sup>18</sup> 2a, e were prepared by reacting the Na-salts of *para*-substituted benzoylacetaldehydes with the hydrochlorides of the appropriate amines.

1-(4-Methoxyphenyl)-3-(1-pyrrolidinyl)-prop-2-enone: (2b), yield 75 %, mp. 96° <sup>1</sup> H NMR: 1.8–2.1 (4H, m), 3.2–3.6 (4 H, m), 3.81 (3 H, s), 5.66 (1 H, d, J = 12.2 Hz), 6.90 (2 H, d, J = 9.0 Hz), 7.93 (2 H, d, J = 9.0 Hz), 8.00 (1 H, d, J = 12.2 Hz). <sup>13</sup>C NMR: 186.94 (C = 0). (Found: C, 72.66, H, 7.34, N, 6.04; O, 13.96. Calc.: C, 72.70; H, 7.41: N, 6.06; O, 13.83 "a).

(1-(4-Bromophenyl)-3-(1-pyrrolidinyl-prop-2-enone; (2c), yield 77  $^{\prime\prime}_{in}$ , mp. 128°  $^{1}$ H NM R: 1.5-1.8 (6 H, m), 3.2-3 5 (4 H, m), 3.83 (3 H, s), 5.82 (1 H, d, J = 12.2 Hz), 6.91 (2 H, d, J = 8.6 Hz), 7.79 (1 H, d, J = 12.2 Hz), 7.93 (2 H, d, J = 8.6 Hz).  $^{13}$ C NMR: 187.18 (C = 0). (Found: C, 55.15; H, 5.16; Br, 28,96, N, 4.98; O, 5.75, Calc.; C, 55.73; H, 5.04; Br, 28.52; N, 5.00; O, 5.71<sup>10</sup> n).

General procedure for preparation of enamino-thiones

0.005 mole 1, suspended in anhyd benzene, was added to 0.01 mole 2, at room temp with sitrring. When the reaction was completed (tlc) the solvent was evaporated under reduced pressure. The residue was dissolved in  $CH_2Cl_2$  and poured into 100 ml 0.05 M NaOH. The aqueous phase was extracted several times with  $CH_2Cl_2$  and the combined  $CH_2Cl_2$  extracts, after evaporation under reduced pressure, were placed on a column (Al<sub>2</sub>O<sub>3</sub>) and eluted with 75°,  $CH_2Cl_2$ /light petroleum. The compounds 3 were recrystallized from THF/light petroleum.



9 :  $R = CH_3$ 

11 :  $R = CH_3$ 

Enamino- thione	Alkyl halide R'X	Yield (%)	mp , /°:	
<b>8</b> a	CH3 I	94 <sup>a)</sup>	218	
8b	CH3 CH5 I	(*10)	160	
8 c	Сан <sub>а</sub> сн <sub>а</sub> т	87 <sup>a)</sup>	214	
9 a	CH3 I	82 <sup>b</sup> )	230	
<b>9</b> 6	снзснэт	87 <sup>b)</sup>	167	
<b>9</b> c	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> T	83 <sup>b)</sup>	205	

a)<sub>Compounds</sub> 10a-10c.

b) Compounds 11a-11c.

Comp.	Analyses (%) Found (Calc.)						
4 + 5	c	н	Br	N	0	s	I
a <sup>1)</sup>	45.58 (46.80)	5.03 (5.05)		3.87 (3.90)		8.98 (8.92)	(35.33)
ъ	46.02 (46.28	5.16 (5.18		3.67 (3.60)	(4.11)	8.33 (8.24)	32.53 (32.60)
c	38.40 (38,38)	3.93 (3.91)	(18.24)	3.21 (3.20)		7.51 (7.32)	29.08 (28.90)
d	48.22 (48.26)	5.37 (5.40)		3.80 (3.75)		8.64 (8.59)	34,04 (34,00)
	47.60 (47.65)	5.62 (5.50)		3.46 (3.47)	(3.97)	8.32 (7.95)	31.80 (31.46)
f <sup>2)</sup>	39.87 (39.84)	4.26 (4.2)	(17.67)	3,18 (3,10)		7.28 (7.09)	28,13 (28,06)
B	(48.26)	5.50 (5.40)		3.57 (3.75)		8,29 (8,59)	32.58 (34.00)
h	48.37 (47.65)	5.43 (5.50)		3.40 (3.47)	(3.97)	8,50 (7,95)	30.20 (31.46)
i	39.74 (39.84)	4.23 (4.23)	(17.67)	3.07 (3.10)		7.19 (7.09)	27.84 (28.00)
j	49.66 (49.62)	5.68 (5.72)		3.34 (3.62)		8.29 (8.28)	32.32 (32.76)
k	49.24 (48.92)	5.97 (5.80)		3.31 (3.36)	(3.83)	7.88 (7.68)	30,48 (30,41)
1	40.39 (41.22)	4.56 (4.54)	(17.14)	2.91 (3.00)		6.77 (6.88)	27.20 (27,22)

Table 5. Analytical data of iminium iodides 4/5

1) 5a: E-1-Pyrrolidinium-(Y-(methylthio)-cinnamylidene) iodide.

2) 4f: Z-1-piperidinium-(p-bromo-Y-(methylthio)-cinnamylidene) iodide.

Table 6. Physical and analytical data of the hexahydroquinolinium halides" 10a-c and 11a-c

Comp.	t/ppm	Analyses (4) Found (Calc.)					
	1°C NMR (C-4)	с	н	N	s	1/8r <sup>b</sup>	
10.4	171,62	40,04 (49,88)	5.14 (5.23)	3.nl (3.64)	8,42 (8,32)	12.03 (12.95)	
10 b	171.86	50.53 (51.13)	5.58 (5.55)	3.41 (3.51)	8.14 (8.03)	30.04 (31.78)	
10 с <sup>ъ)</sup>	172.04	63.56 (63.76)	5+81 (5-84)	3.37 (3.38)	7.87 (7.74)	19,36 (19,28)	
11 a	170,89	51.24 (51.13)	5.58 (5.55)	3.51 (3.51)	8.21 (8.03)	31.74 (31.78)	
11 6	171.01	52.67 (52.30)	5.95 (5.85)	3.40 (1,30)	7.78 (7.76)	29.75 (30.70)	
11, <sup>b)</sup>	171,14	63,40 (64,48)	6.11 (6.12)	3.27 (3.27)	7.32 (7.48)	(18.1.5)	

 a) 10 at N-phenyl-2,3,5,6,7,8-hexahydro-4-methylthio-quinolinium indide,

b) Br-analysis.

*Compound* **3b.** 1-(4-Methoxyphenyl)-3-(1-pyrrolidinyl)prop-2-enthione; mp. 153° (lit.<sup>17</sup> 173°); <sup>13</sup>C NMR: 211.71 (C = S). (Found: C. 67.72; H. 6.76; N. 5.68; O. 6.43, S. 12.89. Calc.: C. 67.98; H. 6.93; N. 5.66; O. 6.47; S. 12.96.

Compound 3c. 1-(4-Bromophenyl)-3-(1-pyrrolidinyl-prop-2-enthione: mp.  $170^{\circ}$ ; <sup>13</sup>C NMR; 211.42 (C = S).

Compound 3e. 1-(4-Methoxyphenyl)-3-piperidino-prop-2enthione; mp. 173;  $^{13}$ CNMR: 212.84 (C = S).

Compound 3f. 1-(4-Bromophenyl)-3-piperidino-prop-2enthione; mp. 173;  $^{13}$ C NMR: 212.23 (C = S).

The compounds 3a, 3d, 8 and 9 have been described earlier.<sup>1</sup>

Alkylation of enamino-thiones. To 0.5 g of enamino-thiones 3, 8 or 9, dissolved in 10 ml CH<sub>3</sub>CN was added 1.0 g of the appropriate alkyl halide with stirring at room temp. After 24 hr the solvent was evaporated under reduced pressure, followed by suspension of the residue in ether. The ppt was filtered off and dried.

The iminium iodides 4/5 and hexahydro-quinolinium iodides 10 and 11 were all characterized by means of IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and micro analyses. Mass spectroscopy showed for the compounds 10 and 11 the hexahydroquinolinium cation, while the iminium cations were not observed for the compounds 4 and 5.

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