Pyridinethiones. VI. The Synthesis of 2*H*-Thiopyrano[2,3-*b*]pyridin-2-ones

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A general and versatile method for the preparation of 2*H*-thiopyrano[2,3-*b*]pyridin-2-ones is described. The starting materials, the β,β-disubstituted vinyl-1-*t*-butyl-2-(1*H*)pyridinethiones were prepared from the synthon 3-formyl-1-*t*-butyl-2-(1*H*)pyridinethione by condensation. ^{13}H nmr spectra showed the vinyl double bond of the condensation products to have the *trans* configuration with the smallest group close to the sulfur atom. Some reactions of these new azaanalogues of thiocoumarins are reported.

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We have previously reported (1) the preparation of a few thiopyrano[2,3-*b*]pyridines (**5**) from 1-*t*-butyl-3-formyl-2-(1*H*)pyridinethione (**1b**) *via* the Wittig-Horner reaction. This method was not general and work up of the reaction products was difficult, the condensation products reported in reference 1 are mixtures of *cis*- and *trans*- isomers. Therefore we now report an improved and general method for the preparation of various 3-vinyl-1-*t*-butyl-2-(1*H*)-pyridinethiones (**2**), a study of the conformation of these synthons and the cyclization reactions of **2**.

The Knoevenagel condensation is the most widely applicable method for the preparation of coumarins. Meth-Cohn and Tarnowski (2) have prepared a number of thiocoumarins by this route, mainly from malonic acid derivatives and 2-(*S*-*t*-butyl)mercaptobenzaldehyde which is a stable derivative of *o*-mercaptobenzaldehyde.

Table 1

Preparation of 3-(2,2-Disubstituted vinyl)-1-substituted 2-(1*H*)pyridinethiones (2)

Compound No. **2**	Molecular Formula	-R	-Z_1	-Z_2	Reaction Conditions Temperature/time (a)	Yield %	Mp (°C) (solvent) (b)	% Found, (Calcd) C	H	N	S
2a	$C_{15}H_{11}N_3OS$ (281.35)	C_6H_5	CN	$CONH_2$	rt 15 hours	94	194-196	63.70 (64.03)	4.14 (3.95)	14.56 (14.93)	11.30 (11.40)
2b	$C_{17}H_{14}N_2O_2S$ (310.40)	C_6H_5	CN	$CO_2C_2H_5$	rt ¾ hour	93	125-127	65.75 (65.78	4.57 (4.56)	8.93 (9.03)	10.49 (10.33)
2c	$C_{20}H_{14}N_2S$ (314.40)	C_6H_5	CN	C_6H_5	rflx 10 minutes	75	154-156 (toluene)	76.26 (76.40)	4.60 (4.49)	8.95 (8.91)	
2d	$C_{14}H_{11}NO_2S$ (257.30)	C_6H_5	H	COOH	70°, 1 hour	93	242-245 dec (ethanol)	65.34 (65.35)	4.48 (4.31)	5.25 (5.45)	12.55 (12.46)
2e	$C_{13}H_{17}N_2O_2S$ (251.35)	t-C_4H_9	CH_3	COOH	85-90°, 7 hours	56	229-232 (ethanol)	62.11 (62.12)	6.74 (6.82)	5.62 (5.57)	
2f	$C_{15}H_{18}N_2O_2S$ (290.37)	t-C_4H_9	CN	$CO_2C_2H_5$	rt 15 hours	95	121-123 (toluene/ benzin 80-110°)	62.12 (62.04)	6.19 (6.25)	9.54 (9.65)	11.24 (11.04)
2g	see reference 1	t-C_4H_9	$CO_2C_2H_5$	$CO_2C_2H_5$	rt 15 hours	87	77.5-79				
2h	$C_{13}H_{15}N_3OS$ (261.34)	t-C_4H_9	CN	$CONH_2$	rt 15 hours	87	170-172	59.68 (59.74)	5.85 (5.79)	15.95 (16.08)	12.05 (12.27)
2i	$C_{13}H_{13}N_3S$ (243.32)	t-C_4H_9	CN	CN	rt 2 hours	85	152-154	64.00 (64.17)	5.56 (5.38)	17.09 (17.27)	13.40 (13.18)
2j	$C_{21}H_{23}NO_3S$ (369.46)	t-C_4H_9	$CO_2C_2H_5$	COC_6H_5	rflx 10 minutes	87	149-151	68.31 (68.26)	6.25 (6.27)	3.70 (3.79)	8.62 (8.68)
2k	$C_{16}H_{17}N_3O_2S$ (279.36)	t-C_4H_9	$CONH_2$	$CONH_2$	rflx 4 hours	57	180-181 (methanol)	55.78 (55.89)	6.08 (6.13)	14.89 (15.03)	11.62 (11.48)
2l	$C_{18}H_{18}N_2S$ (294.41)	t-C_4H_9	CN	C_6H_5	rt 1½ hours	85	127-129	73.24 (73.43)	5.99 (6.16)	9.46 (9.52)	11.00 (10.89)
2m	$C_{19}H_{18}N_2OS$ (322.42)	t-C_4H_9	CN	COC_6H_5	rt ½ hour	54	133-134 (ethyl acetate)	70.72 (70.77)	5.64 (5.63)	8.61 (8.69)	
2n	$C_{14}H_{10}N_2S$ (238.31)	H	CN	C_6H_5	rt 72 hours	71	212-213 (ethanol)	70.10 (70.56)	4.60 (4.23)	11.61 (11.76)	

(a) rt = room temperature, rflx = reflux. (b) When no solvent is given, the products were analytically pure.

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Table 2

Spectral Data of 3-(2,2-Disubstituted vinyl)-1-substituted-2-(1*H*)pyridinethiones (2)
^{1}H Chemical Shift (a)

Compound	UV (absolute ethanol) λ max (log ε)	H>C=C<	H(4)	H(5)	H(6)	other protons
2a	414 (3.60), 334 (3.94), 246 (4.15)	8.83 (s)	8.13 (d) J = 7	7.07 (t) J = 7	8.32 (d) J = 7	7.88 (br, -NH_2), 7.53 (s, -C_6H_5)
2b	437 (3.57), 342 (3.88), 261 (4.08)	8.75 (s)	8.23 (d) J = 7	7.12 (t) J = 7	8.37 (d) J = 7	1.32 (t, -CH_3 J = 7.4), 4.36 (q, -CH_2 J = 7.4), 7.55 (s, -C_6H_5)
2c	410 (3.69), 332 (4.19), 264 sh (4.20), 240 sh 224 sh	8.10-8.30	8.10-8.30	7.09 (t) J = 7	8.10-8.30	7.5-8.0 (m) 2-C_6H_5
2d	413 (3.53), 324 (3.98), 240 (4.20)	8.32 (d) J = 16	7.9-8.15	6.46 (t) J = 7	8.15-7.9	6.46 (d) =CH *trans*- J = 16, 7.5 (m) -C_6H_5
2e	385 (3.82), 322 (4.04), 239 (4.11), 216 (4.20)	7.85 (s)	7.30-7.75	6.87 (t) J = 7	8.03 (d) J = 7	7.3-7.75 (m) -C_6H_5, CH, 12 (br) -COOH, 1.9 (s) -CH_3
2f	419 (3.80), 345 (4.07), 264 (4.16)	8.73 (s)	7.77 (d) J = 7	6.77 J = 7	8.18 J = 7	4.38 (q) -CH_2 J = 7, 2.00 (s) *t*-C_4H_9, 1.37 (t) -CH_3 J = 7
2g	see reference 1	8.17 (s)	7.37 (s) J = 7	6.62 (t) J = 7	8.09 (d) J = 7	~4.27 (m) -CH_2-, 2.03 (s) *t*-C_4H_9, 1.07-1.57 (m)-CH_3
2h	405 (3.81), 339 (4.11), 258 (4.15) 214 (4.23)	8.40 (s)	7.85 (d) J = 7.2	6.98 (t) J = 7.2	8.48 (d) J = 7.2	7.8 (b) -NH_2, 2.00 (s) *t*-C_4H_9
2i	423 (3.76), 354 (4.03), 265 (4.14)	8.38 (s)	7.76 (d) J = 7	6.82 (t) J = 7	8.25 (d) J = 7	2.03 (s) -*t*-C_4H_9
2j	390 sh, (3.90), 340 (4.01), 252 (4.37)	8.30 (s)	7.80-8.07	6.40 (t)	7.80-8.07	7.13-7.47 (m) -C_6H_5, 4.27 (q) -CH_2 J = 7.2, 2.00 (s) *t*-C_4H_9, 1.23 (t) -CH_3 J = 7.2
2k	383 (3.91), 327 (4.01), 245 sh	7.73 (s)	7.54 (d) J = 7	6.83 (t) J = 7	8.30 (d) J = 7	7.27 (br) -NH_2, 2.07 (s) *t*-C_4H_9
2l	400 (3.82), 337 (4.12), 271 (4.15), 225 (4.19)	7.93 (s)	7.05-7.83	6.49 (t) J = 7.2	7.05-7.83	7.05-7.83 (m) -C_6H_5, 1.82 (s) *t*-C_4H_9
2m	422 (3.76), 3.49 (3.88), 263 (4.17)	8.43 (s)	7.27-8.20	6.75 (t) J = 7	7.27-8.20	7.27-8.2 (m) -C_6H_5, 2.03 (s) *t*-C_4H_9
2n	415 sh, 332 (4.15), 263 sh (3.99), 231 (3.95)	8.17 (d)	7.3-8.1	6.97 (t) J = 7	7.3-8.1	7.3-8.1 (m) -C_6H_5, 14.1 (br) NH

(a) (ppm from TMS); J in Hz; **2f**, **2g**, **2i**, **2j**, **2l** and **2m** deuteriochloroform the rest in DMSO-d_6.

The 3-Vinylpyridinethiones.

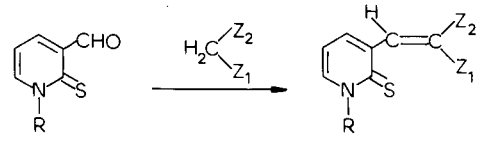
The 3-vinylpyridinethiones (**2**) reported in Table 1 have all been prepared from either 1-*t*-butyl- or 1-phenyl-3--formyl-2-(1*H*)pyridinethione (3) (**1a** or **1b**, see Scheme 1 and Table 1).

In most cases the reactions were performed in absolute ethanol with piperidine (4) as catalyst. The reaction conditions are reported in Table 1. In all cases prepared here only one geometric isomer was found, as seen both from tlc and nmr spectra.

Geometry of the Vinyl Double Bond.

Usually the condensation of benzaldehyde yield acrylonitriles C_6H_5-CH=CXV(X=CN) which have a configuration at the vinyl double bond such that the phenyl group and the smaller of the groups X, are *cis* to one another (5). For the present series of compounds the assignment of the ^{1}H nmr shift values (Table 2) was not of any value for assignment of the configuration (6). Therefore the undecoupled ^{13}C nmr spectra of the condensation products (**2**) were recorded. In some of these spectra the resonance due to the vinylic substituents could easily be found, thus ^{13}C

Scheme 1



1 2

1a R = C_6H_5 $Z_1 \neq Z_2$

1b R = $C(CH_3)_3$

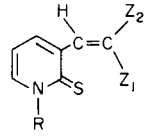
1c R = H

	R	Z_1	Z_2
2a	C_6H_5	CN	$CONH_2$
2b	C_6H_5	CN	$CO_2C_2H_5$
2c	C_6H_5	CN	C_6H_5
2d	C_6H_5	H	CO_2H
2e	$C(CH_3)_3$	CH_3	CO_2H
2f	$C(CH_3)_3$	CN	$CO_2C_2H_5$
2g	$C(CH_3)_3$	$CO_2C_2H_5$	$CO_2C_2H_5$
2h	$C(CH_3)_3$	CN	$COHN_2$
2i	$C(CH_3)_3$	CN	CN
2j	$C(CH_3)_3$	$CO_2C_2H_5$	COC_6H_5
2k	$C(CH_3)_3$	$CONH_2$	$CONH_2$
2l	$C(CH_3)_3$	CN	C_6H_5
2m	$C(CH_3)_3$	CN	COC_6H_5
2n	H	CN	C_6H_5

nmr spectra of these selected examples are given in Table 3, together with the coupling constants for the vinyl double bond. Figure 1 shows the noise decoupled and the gated decoupled ^{13}C nmr spectra of compound **2k**, here the coupling constants for the *cis* and *trans* amide carbons can be seen. Table 3 shows the long range CCCH *trans*-coupling constants to be in the range 9.8-13.7 Hz while the corresponding *cis*-coupling constants are much smaller, 4.9-7.8 Hz. Similar results for long range CCCH coupling constants for vinylic double bonds in acrylic acids have been reported by Marshall and Seiwell (7), namely J_{cis}-CCCH = 6.78 Hz and J_{trans}-CCCH = 14.50 Hz.

Table 3

Selected Values From the Undecoupled ^{13}C NMR Spectra of the Long Range Coupling of the Vinylic System, (in DMSO-d_6)



2

Compound	Shift in ppm	HCCC Coupling	Z_1 and Z_2
			Z_2 = $CONH_2$
2h	162.186	J = 4.9 (*cis*, Z_2)	Z_1 = CN
	113.13	J = 7.8 (*cis*), Z_2)	Z_2 = CN
2i	111.90	J = 13.7 (*trans*, Z_1)	Z_1 = CN
	168.048	J = 9.8 (*trans*, Z_2)	Z_2 = $CONH_2$
2k	165.619	J = 5.1 (*cis*, Z_1)	Z_1 = $CONH_2$
			Z_2 = $COOC_2H_5$
2m	114.749	J = 13.7 (*trans*, Z_1)	Z_1 = CN

For the present series it is seen that the compounds **2i** and **2m** show the long range HCCCN coupling constants corresponding to a *trans*-configuration, which demonstrates that the nitrile moiety is situated *trans* relative to the vinylic hydrogen and consequently the relatively small nitrile moiety is always found close to the sulfur atom.

This geometry was tentatively suggested by Meth-Cohn and Tarnowski (2) on the basis of the yields obtained for the related condensation products from *o*-mercaptobenzaldehyde.

The Cyclisation Reactions.

The cyclisations were all performed by reflux of com-

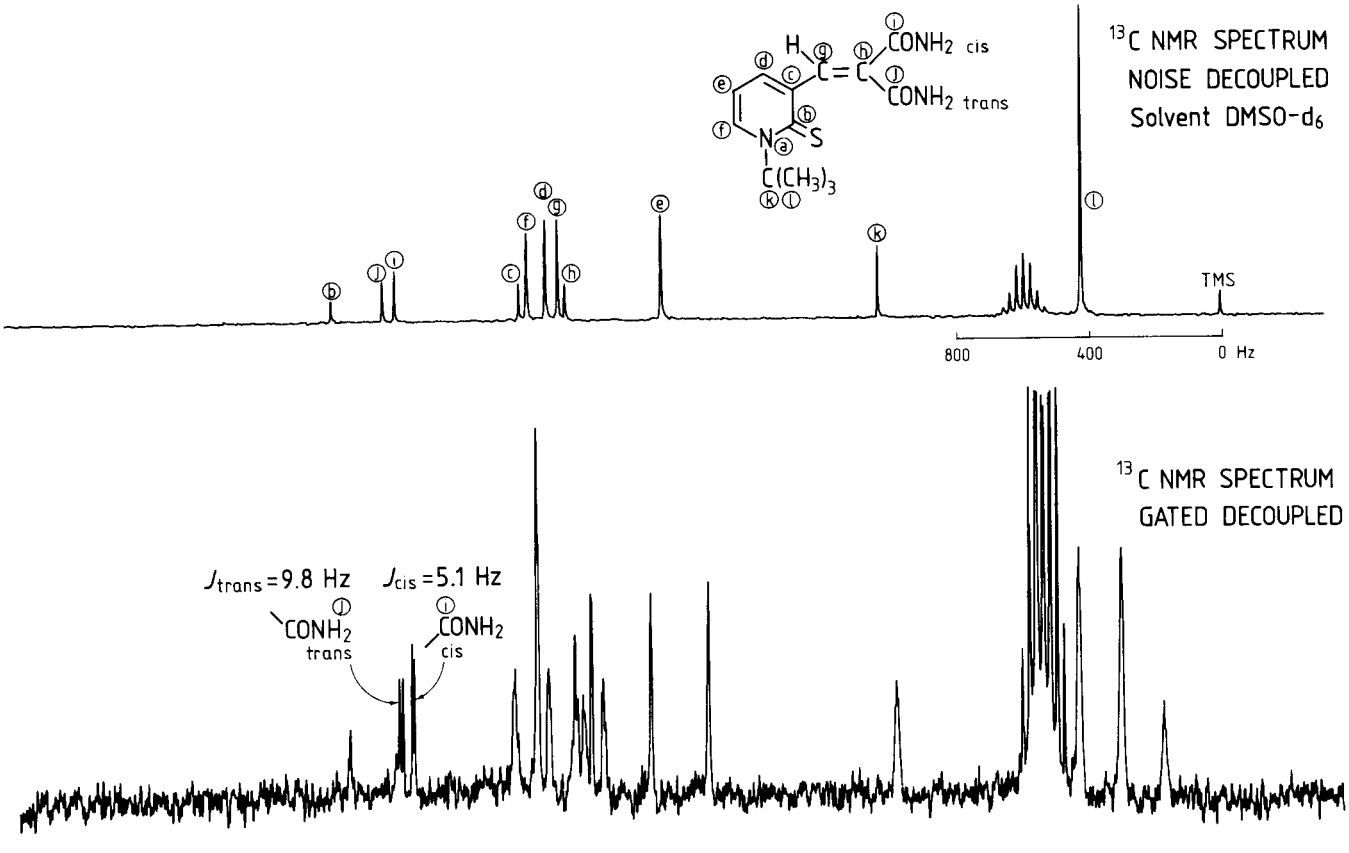
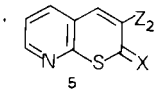


Figure 1. The noise decoupled and the gated decoupled ^{13}C nmr spectra of compound **2k** (J_n DMSO-d_6). Resonance due to the *cis* and *trans*-amide group is indicated in the spectra.

Table 4

2*H*-Thiopyrano[2,3-*b*]pyridines, and Related Compounds



5

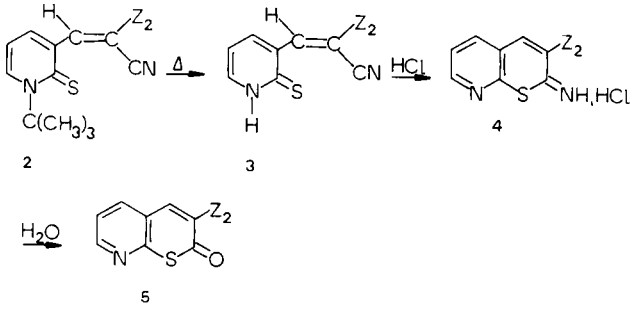
Product	Yield (%) (a)	$-Z_2$	$=X$	Starting Compound	Reaction Condition Temperature/time	mp (°C) solvent	Molecular formula					
5a	65	CN	O	**2i** (b)	80°, 2 minutes	190-192° ethanol	$C_9H_4N_2OS$ (188.21)	Found	C 57.30	H 2.05	N 14.91	S 17.10
								Calcd.	C 57.43	H 2.14	N 14.89	S 17.04
5b	31	$CO_2C_2H_5$	O	**2f**	80°, 2 minutes	136-138° ethanol	previously prepared, see reference 1					
5c	method A, 80 method B, 92	C_6H_5	O	**2l** or **1b**	reflux 15 hours	165-167° analytically pure	$C_{14}H_9NOS$ (239.29)	Found	C 70.19	H 3.59	N 5.85	S 13.32
								Calcd.	C 70.26	H 3.79	N 5.85	S 13.40
5d	91	$CONH_2$	O	**2h**	80°, ½ minute	188-190° 2-propanol	$C_9H_6N_2O_2S$ (206.22)	Found	C 52.50	H 2.97	N 13.47	S 15.80
								Calcd.	C 52.41	H 2.91	N 13.59	S 15.55
5e	44	COC_6H_5	O	**2m**	reflux 20 minutes in concentrated HCl/EtOH 1:1	166-168° ethanol	$C_{15}H_9NOS$ (267.29)	Found	C 67.39	H 3.34	N 5.23	
								Calcd.	C 67.40	H 2.29	N 5.24	
5f	method A, 61 method B, 69	*p*-ClC_6H_4	O	(c) **1b**	reflux 5 minutes	185-187° ethanol	$C_{14}H_8ClNOS$ (273.74)	Found	C 61.42	H 2.95	N 5.12	
								Calcd.	C 61.60	H2.96	N 4.86	
5g	34	$CONHCOCH_3$	O	**5d**	reflux 2 hours	184-186° 2-propanol	$C_{11}H_8N_2O_3S$ (284.25)	Found	C 53.29	H 3.48	N 11.37	
								Calcd.	C 53.23	H 3.25	N 11.29	
5h	70	$NHCOCH_3$	O	**1b**	reflux 10 hours	256-258° toluene	$C_{10}H_8N_2O_2S$ (220.24)	Found	C 54.98	H 3.62	N 12.91	
								Calcd.	C 54.55	H 3.64	N 12.73	
5i	58	$NHCOC_6H_5$	O	**1b**	reflux 10 hours	183-185° toluene	$C_{15}H_{10}N_2O_2S$ (282.32)	Found	C 64.00	H 3.57	N 9.73	
								Calcd.	C 63.88	H 3.55	N 9.93	
4c	91	C_6H_5	NH, HCl	**2l**	10°, 30 minutes	214-217° dec	$C_{14}H_{11}ClN_2S$	unstable, hygroscopic				
7	19	C_6H_5	S	**4c**	110-115° 90 minutes	154-156° 2-propanol	$C_{14}H_9NS_2$ (255.35)	Found	C 65.07	H 3.34	N 5.33	
								Calcd.	C 65.85	H 3.55	N 5.49	
6	54	C_6H_5	NOH	**4c**	20°, 14 days	201-203° ethanol	$C_{14}H_{10}N_2OS$ (254.31)	Found	C 65.98	H 3.91	N 11.04	
								Calcd.	C 66.12	H 3.96	N 11.02	

(a) Recrystallized product. (b) Compounds **2**, see Table 1. (c) Starting material: *p*-$ClC_6H_5CH_2CN$, compound **2** was not isolated.

pounds **2** in concentrated hydrochloric acid (Table 4), the short reaction time for this reagent is remarkable.

In each case it was found that the nitrile group *trans* to the vinyl hydrogen had taken part in the cyclisation. This fact can be taken as a further support for the *trans*-structure assigned to the starting materials. The cyclisation takes place with dealkylation to form isobutene (8), whereupon the intermediately formed imine **4** rapidly is hydrolysed to the azathiocoumarin **5** (Scheme 2, method A).

Scheme 2

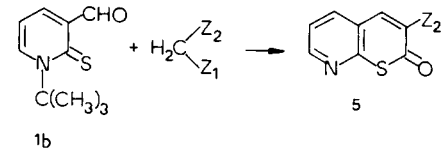


The intermediates usually are not isolated under these reaction conditions, Method A.

For method A the following starting compounds **2** was used:

2i	Z_2 = CN	to give **5a**
2f	Z_2 = $COOC_2H_5$	to give **5b**
2l	Z_2 = C_6H_5	to give **5c**
2h	Z_2 = $CONH_2$	to give **5d**
2m	Z_2 = COC_6H_5	to give **5e**

Scheme 3



Method B:

$H_2CZ_1Z_2$

Z_1 = CN	Z_2 = C_6H_5	gives **5c**
Z_1 = CN	Z_2 = *p*-ClC_6H_4	gives **5f**
Z_1 = COOH	Z_2 = $NHCOCH_3$	gives **5h**
Z_2 = COOH	Z_2 = $NHCOC_6H_5$	gives **5i**

Table 5

Spectral Data of 2*H*-Thiopyrano[2,3-*b*]pyridines, and Related Compounds

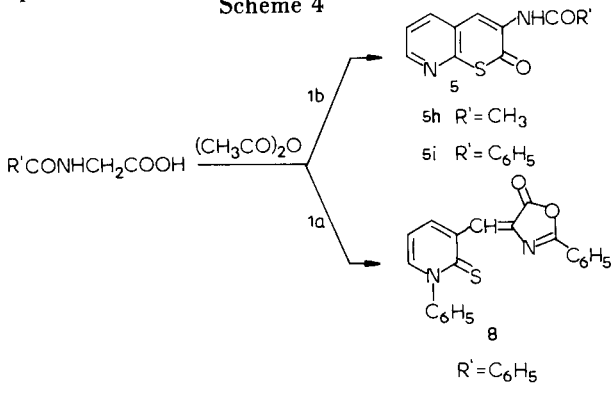
Compound	UV (absolute ethanol) λ max (log ε)	IR (KBr) ν max	^{1}H,Chemical Shift (a) H(4)	H(5)	H(6)	H(7)	Other Protons
5a	358 (3.79), 301 (3.71) 291 (3.70), 263 (3.67) 238 (3.79)	2230 (CN), 1650 (CO)	9.03 (s)	8.42 (dd J = 8, 1.6)	7.66 (dd J = 5, 8)	8.87 (dd J = 5, 1.6)	
5b	reference 1	1740 (CO), 1640 (CO)	8.70 (s)	8.47 (dd J = 8, 1.6)	7.67 (J = 8, 4.8)	8.83 (dd J = 4.8, 1.8)	4.38 (q J = 7 -CH_2) 3.37 (t J = 7 -CH_3)
5c	341 (4.00), 320 sh 229 (4.54)	1620 (CO)	7.70 (s)	7.92 (dd J = 8, 1.5)	7.25	8.62 (dd J = 5, 1.5)	7.5 (m C_6H_5)
5d	350 (3.30), 2.95 sh 288 (3.25), 260 (3.45) 235 (3.84)	1670 (CO), 1630, 1550	8.85 (s)	8.57 (dd J = 7.2, 1.4)	7.60 (dd J = 7.2, 4.5)	8.80 (dd J = 4.5, 1.6)	7.97 (br -NH_2)
5e	341 (3.84), 294 (3.78) 284 (3.80), 250 sh, 229 (5.50)	1655 (CO), 1630 (CO)	7.3-8.1	7.3-8.1	7.3-8.1	8.73 (dd J = 4.4, 1.4)	7.3-8.1 (m -C_6H_5)
5f	341 (4.07), 316 sh 229 (4.61)	1620 (CO)	7.73 (s)	8.00 (dd J = 8, 1.2)	7.3-7.6	8.73 (dd J = 4.4, 1.2)	7.3-7.6 (m -C_6H_4)
5g	335 (3.73), 295 (3.58) 262 sh (3.92), 238 (4.36)	1750 (CO), 1690 1610, 1500	8.55 (s)	8.50 (dd J = 8, 2)	7.66 (dd J = 8, 5)	8.87 (dd J = 5, 2)	11.2 (br -NH) 2.23 (s -CH_3)
5h	355 sh (4.00), 340 (4.17), 314 sh (3.92), 255 sh (4.00), 277 (4.39)	1610, 1710 (CO)	8.96 (s)	7.93 (dd J = 8, 1.7)	7.34 (dd J = 8, 4.6)	8.58 (dd J = 4.6, 1.7)	2.26 (s -CH_3) 8.26 (sb -NH)
5i	358 (4.13), 343 (4.28), 314 (4.05), 302 sh 258 sh (4.11), 234 (4.42)	1615, 1666, 1718 (CO)	9.13 (s)	7.99	7.24 m	8.59 (dd J = 4.6, 1.7)	7.99-7.24 m
4		1620 (CNH)	8.40 (s)	8.63 (d J = 8)	7.80 (dd J = 4.4, 8)	8.93 (d J = 4.4)	7.63 (s -C_6H_5) 9-10 (br =NH; 2HCl)
7	423 (4.03), 309 (3.82) 276 sh (3.99), 263 sh (4.09) 238 (4.37), 230 (4.37)	1120 (CS)	8.00 (s)	8.33 (d J = 7.6)	7.50 (dd J = 4.4, 7.6)	8.72 (d J = 4.4)	7.42 (s -C_6H_5)
6	352 (3.96), 241 (4.44)	1410	6.97 (s)	7.80 (d J = 7)	7.23 (dd J = 5, 8.5)	8.33 (d J = 4.4)	7.40 (s -C_6H_5) 12.43 (s =NOH)

(a) (ppm from TMS), J in Hz, **4c**, **5e**, **5h** and **5i** in deuteriochloroform, the rest in DMSO-d_6.

An alternative "one pot" synthesis (Scheme 3) was also worked out for the azathiocoumarin **5** (method B) in which the condensation product **2** was not isolated, but directly cyclised to **5** in yields comparable to the stepwise method.

If **1a** is treated with an *N*-acylated glycine under similar reaction conditions an azlactone **8** is formed in high yield while the Perkin reaction with an *N*-acylated glycine and **1b** (method C) directly gives the ring system **5** (Scheme 4) as expected.

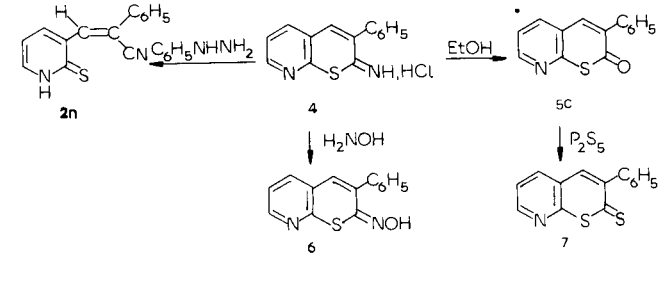
Scheme 4



Formation of an imine in this type of reaction was tentatively suggested by Meth-Cohn and Tarnowski (2) in the related preparation of thiocoumarins. Evidence for the formation of imine **4** was obtained in the present synthesis of azathiocoumarins when a solution of **2l** in dioxane was treated with dry hydrogen chloride, whereby the hydrochloride of the imine (**4**) was immediately precipitated.

This reactive imine was characterised by spectra and by transformation into the oxime **6** with hydroxylamine.

Scheme 5



Reaction of **4** with phenylhydrazine resulted in ring opening to give **2o**, while reflux in ethanol resulted in conversion to the thiolactone **5c**. Treatment of **5d** with acetic anhydride yielded the amide **5g**, while reaction of **4** with phosphorus pentasulfide resulted in the expected formation of thione **7**.

EXPERIMENTAL

Microanalyses were carried out in the microanalytical Department of the University of Copenhagen by Mr. P. Hansen or at NOVO A/S, Copenhagen.

The instrumentation is the following: ^{1}H nmr, Jeol JNM-PMX 60, ^{13}C nmr, Jeol FX 60; mp Büchi apparatus (uncorrected); ir, Perkin Elmer 580; uv, Varian Cary 219.

3-(2,2-Disubstituted-vinyl)-1-*t*-butyl-2-(1*H*)pyridinethiones or 3-(2,2-disubstituted-vinyl)-1-phenyl-2-(1*H*)pyridinethiones Compounds **2a,b,f,g,h,i,j** and **k**. General procedure.

1-Phenyl-3-formyl-2-(1*H*)pyridinethione (**1a**, 2.15 g, 0.01 mole) or 1-*t*-butyl-3-formyl-2-(1*H*)pyridinethione (**1b**, 1.95 g, 0.01 mole) was mixed with the active methylene compound (H_2C Z_2, see Table 1, 0.01 mole) in ethanol (20 ml). Piperidine (0.2 ml) was added and the mixture was heated with stirring according to Table 1. The precipitated crystalline product, which in most cases was analytically pure, was washed with ether, dried and recrystallized.

Special Procedures.

Compounds **2c** and **2l**.

An ethanolic solution of sodium ethoxide (1.2 ml, 2*M* was added to a mixture of 1-phenyl-3-formyl-2-(1*H*)pyridinethione (**1a**, 2.15 g, 0.01 mole) or 1-*t*-butyl-3-formyl-2-(1*H*)pyridinethione (**1b**, 1.95 g, 0.01 mole) in absolute ethanol (15 ml) with benzyl cyanide (1.17 g, 0.01 mole). The mixture was stirred at room temperature for 1.5 hours, whereupon addition of ether gave a yellow crystalline product which was filtered and recrystallized from toluene.

Compound **2d**.

1-Phenyl-2-formyl-2-(1*H*)pyridinethione (**1a**, 2,15 g, 0.01 mole), malonic acid (1.1 g, 0.01 mole) and piperidine (2 ml, 0.02 mole) was dissolved in pyridine (4) (10 ml). The mixture was stirred at 70° for one hour, and poured into a mixture of ice (100 g) and hydrochloric acid (12 ml 4*M*). The yellow precipitate was filtered, washed with water, dried and recrystallized from absolute ethanol.

Compound **2e**.

1-*t*-Butyl-2-(1*H*)pyridinethione (**1b**, 1.95 g, 0.01 mole) and methylmalonic acid (2.36 g, 0.02 mole) was dissolved in a mixture of pyridine (4) (15 ml) and piperidine (2 ml, 0.02 mole). The mixture was stirred at 85-90° for 7 hours and overnight at room temperature whereupon the reaction mixture was poured into a mixture of concentrated hydrochloric acid (25 ml) and ice (50 g). The precipitated yellow crystals were washed with water, dried and recrystallized from ethanol (96%).

2*H*-Thiopyrano[2,3-*b*]pyridin-2-ones (**5**). General procedure.

Method A.

The appropriate 1-*t*-butyl-3-(2,2-disubstituted-vinyl)-2-(1*H*)pyridinethione (**2**) was heated in concentrated hydrochloric acid according to Table 4. Excess hydrochloric acid was evaporated *in vacuo* (maximum bath temperature 80°) and the solid residue washed with sodium carbonate (2*M*) and water. The crude product was then dried and recrystallized.

Method B.

("One pot" Syntheses) **5c** and **5f**.

1-*t*-Butyl-3-formyl-2-(1*H*)pyridinethione (1) (**1b**, 1.95 g, 0.01 mole), benzyl cyanide (0.01 mole) (to prepare **5c** or *p*-chlorobenzyl cyanide, to prepare **5f** (0.01 mole) respectively and sodium ethoxide solution (1 ml, 1*M*) was mixed in absolute ethanol (10 ml) and refluxed for 20 minutes. After cooling, concentrated hydrochloric acid (10 ml) was added and the mixture refluxed for 1 hour. The white precipitate which formed after cooling was filtered, washed with water, dried and recrystallized.

3-Phenyl-2*H*-thiopyrano[2,3-*b*]pyridine-2-imine Hydrochloride (**4c**) (Z_2 = C_6H_5).

A solution of 1-*t*-butyl-3-(2-phenyl-2-cyanovinyl)-2-(1*H*)pyridinethione (**21**, 1.0 g, 0.0034 mole) in dry dioxane (10 ml) was saturated with dry hydrogen chloride. The mixture was left at 0° for 30 minutes, whereupon the white precipitate was filtered and dried (80° *in vacuo*), yield of **4c** 0.9 g (91%), mp 214-217° dec. Attempted recrystallization from ethanol resulted in quantitative hydrolysis to **5c**.

3-Phenyl-2*H*-thiopyrano[2,3-*b*]pyridine-2-ketoxime (**6**).

Hydroxylammonium chloride (0.1 g, 0.0015 mole) was added to a solution of **4** (0.3 g, 0.001 mole) in pyridine (6 ml) and absolute ethanol (6 ml). This mixture was heated on a steam bath until all dissolved and left for 14 days whereupon the product **6** was isolated as yellow prisms and recrystallized from ethanol.

3-Phenyl-2*H*-thiopyrano[2,3-*b*]pyridine-2-thione (**7**).

3-Phenyl-2*H*-thiopyrano[2,3-*b*]pyridin-2-one (**5c**) was mixed with phosphorus pentasulfide (2.0 g) and toluene (10 ml). The mixture was stirred at 100-115° for 90 minutes. The hot supernatant was decanted and the black residue extracted with hot toluene (3 × 10 ml). Concentration *in vacuo* of the combined toluene extracts yielded a brown residue. This residue was extracted with methanol and the methanol phase was filtered through silica. Concentration to *ca.* 10 ml yielded dark red crystals of **7** which was recrystallized from 2-propanol.

3-(*N*-Acetylcarbamoyl)-2*H*-thiopyrano[2,3-*b*]pyridin-2-one (**5g**).

3-Carbamoyl-2*H*-thiopyrano[2,3-*b*]pyridin-2-one (**5d**), (0.4 g, 0.002 mole) was suspended in acetic anhydride (4 ml) and hydrogen iodide (57%, 3 drops). Reflux for 2 hours and cooling yielded a precipitate of brown crystals. Filtering, washing with ether and drying gave 0.17 g (34%) of **5g** as tan coloured crystals which could be recrystallized from 2-propanol.

3-Acetamido-2*H*-thiopyrano[2,3-*b*]pyridin-2-one (**5h**).

Method C.

1-*t*-Butyl-2-(1*H*)pyridinethione (**1b**, 1.95 g, 0.01 mole) was refluxed for 10 hours with *N*-acetylglycine (1.2 g, 0.01 mole) and anhydrous sodium acetate (0.82 g, 0.01 mole) in acetic anhydride (20 ml). The crystals which precipitated after cooling to room temperature were filtered, washed with icecold ethanol and pentane, yield 1.54 (70%) tan coloured crystals. Recrystallization from toluene gave pale yellow needles mp 256-258°.

3-Benzamido-2*H*-thiopyrano[2,3-*b*]pyridin-2-one (**5i**).

Method C.

This compound was prepared as described above, thus **1b** (0.001 mole), hippuric acid (1.9 g, 0.011 mole), sodium acetate (0.82 g, 0.01 mole) in acetic anhydride yielded 1.64 g (58%) of the title compound as grey crystals. Recrystallization from toluene gave pale red needles mp 183-185°.

3-(2-Phenyl-2-cyanovinyl)-2*H*-pyridinethione (**2n**).

Phenylhydrazine (0.3 ml, 0.027 mole) in ethanol (1 ml) was added to a suspension of the hydrochloride **4c** (0.4 g, 0.0013 mole) in pyridine (0.5 ml) and ethanol (3 ml). The mixture was heated on a steam bath until all dissolved and left for 3 days at room temperature. The orange crystals were then isolated and recrystallized from absolute ethanol to give **2o**, yield 0.22 g (71%), mp 211.5-213°.

Azlactone of 1-phenyl-2-(1*H*)pyridinethione-3-carbaldehyde (**8**).

1-Phenyl-3-formyl-2-(1*H*)pyridinethione (**1a**, 4.3 g, 0.02 mole) and *N*-benzoylglycine (3.8 g, 0.021 mole) was refluxed in acetic anhydride (40 ml) for 10 hours, followed by stirring at room temperature for 24 hours. The precipitated crystals were filtered, washed with 96% ethanol and dried, yield 4.2 g (59%) of brick red crystals of **8**, mp 256 258° dec/ethyl cellosolve.

Anal. Calcd. for $C_{21}H_{14}N_2O_2S$: C, 70.38; H, 3.94; N, 7.82. Found: C, 70.67; H, 4.05; N, 7.59.

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