One-Pot Synthesis of 4-Acylimino-2-aminothieno[2,3-*d*][1,3]-thiazines from 2-Thioureidothiophene-3-carbonitriles [1]

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A new one-pot synthesis of 4-acylimino-2-aminothieno[2,3-*d*][1,3]thiazines **4** and **5**, respectively, from 2-thioureidothiophene-3-carbonitriles **1**, acetic, propionic anhydride, respectively, and concentrated sulfuric acid is reported. The structure of **4a** is confirmed by X-ray structure analysis.

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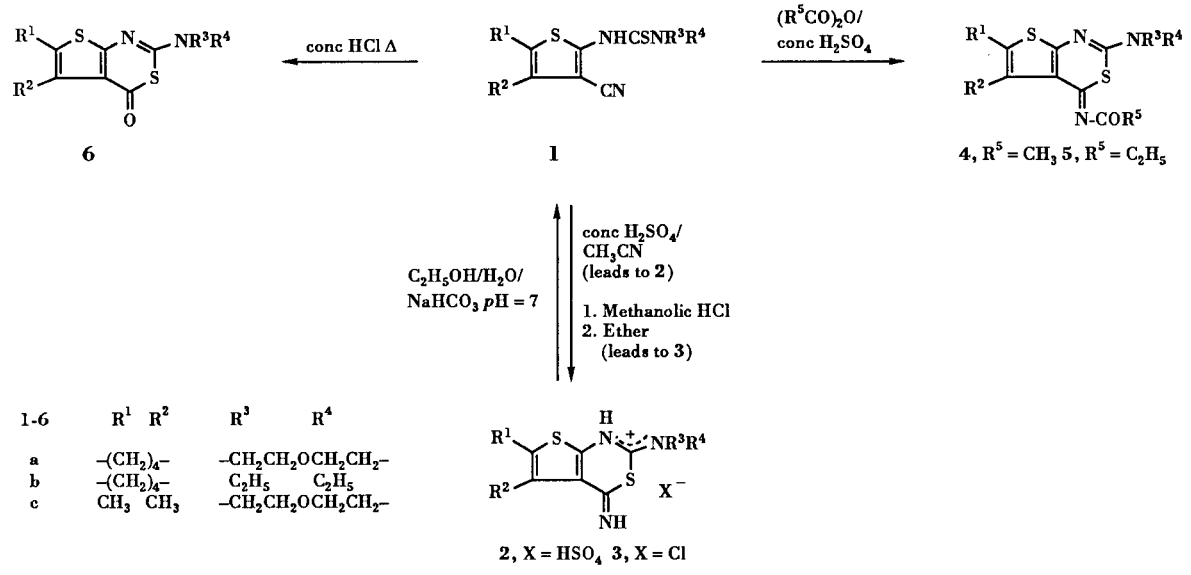
In a previous paper we reported on the synthesis of various substituted 2-aminothieno[2,3-*d*][1,3]thiazin-4-ones of the type **6** from ethyl thioureidothiophene carboxylates by action of concentrated sulfuric acid [3]. On the other hand, recently we reported, that benzoylthioureidothiophenecarbonitriles **1** (R^3 = H, R^4 = COC_6H_5) on treatment with concentrated sulfuric acid undergo cyclization involved by debenzoylation to the intermediate 2-amino-4-iminothienothiazinium hydrogen sulfates, followed by a ring opening reaction to give thioureidothiophenecarbonitriles **1** (R^3 = R^4 = H) [4].

In the courses of our investigations directed toward the synthesis of anellated 1,3-thiazines [5] we describe in this paper the reaction of 2-thioureidothiophene-3-carbonitriles **1** under different acid conditions and a convenient procedure for the preparation of the title compounds **4** and **5**. Three thioureidocarbonitriles **1a-c**, prepared from 2-isothiocyanatothiophene-3-carbonitriles and morpholine, diethylamine, respectively, were the starting material for these investigations.

The treatment of **1a-c** with concentrated sulfuric acid at room temperature and addition of water leads to coloured solutions. Subsequently, after neutralization the starting compounds **1** have been separated in each case. We suggested that this reaction proceeds *via* 2-amino-4-iminothiazinium hydrogen sulfates **2**. In order to separate the thiazinium hydrogen sulfates, solutions of **1a-c** in acetonitrile were treated with sulfuric acid. The resulting salts **2a-c** could be isolated in moderate yields. Upon treatment with methanolic hydrochloric acid under mild conditions the cyclization of **1a-c** proceeds readily to give the thiazinium chlorides **3a-c**. 2-Amino-4-iminothieno[2,3-*d*][1,3]thiazines appear to be stable only in form of their salts. However, aqueous-ethanolic solutions of thiazine salts **2** or **3**,

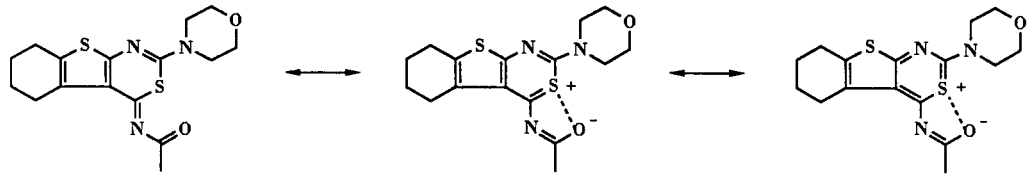
Scheme 1



6 **1** **4**, R^5 = CH_3 **5**, R^5 = C_2H_5

2, X = HSO_4 **3**, X = Cl

Scheme 2



respectively, were carefully neutralized, the corresponding thioureidocarbonitriles of type **1** were obtained. A few comparable ring cleavage reactions of (anellated) 4-imino-1,3-thiazines or -1,3-oxazines, respectively, preferably under basic conditions, resulting the corresponding carbonitriles have been described [6,7].

Table 1

Compounds 1-6 Prepared

Product	Yield (%)	Mp [°C] (solvent)	Molecular Formula or Lit mp [°C]	Analysis (Calcd./Found) C	H	N	S	IR (KBr) [cm^{-1}] ν C=O	ν C≡N	UV (Ethanol) λ max [nm] (log ε)
1a	88	170-172 (*n*-hexane/CH_2Cl_2)	169-170 [19]	54.69 54.70	5.57 5.44	13.67 13.72	20.86 21.03	–	2200	243 (4.08), 269 (3.04), 368 (3.99)
1b	58	105-107 (cyclohexane)	100-101 [19]	57.30 57.53	6.53 6.63	14.32 14.49	21.85 21.65	–	2200	253 (4.07), 317 (3.79)
1c	89	164-168 (*n*-hexane/CH_2Cl_2)	$C_{12}H_{15}N_3OS_2$ (281.4)	51.22 51.07	5.37 4.99	14.93 14.49	22.79 21.65	–	2200	262 (4.07), 320 (3.89), sh 370 (3.34)
2a	66	>135 dec	$C_{14}H_{19}N_3O_5S_3$ (405.5) [a]	41.46 41.49	4.72 5.06	10.36 10.13	23.72 23.20	–	–	247 (4.25), 279 (4.28), sh 315 (3.84), 427 (3.82)
2b	74	153-155	$C_{14}H_{21}N_3O_4S_3$ •1/2 H_2O (400.5)	41.89 41.84	5.54 5.66	10.49 10.63	24.02 23.81	–	–	246 (4.27), 278 (4.26), sh 316 (3.82), 425 (3.82)
2c	44	152-154	$C_{12}H_{17}N_3O_5S_3$ •3 H_2O (433.5) [b]	33.24 32.88	5.35 5.13	9.69 9.20	22.19 22.68	–	–	246 (4.22), 278 (4.24), sh 313 (3.80), 425 (3.79)
3a	85	>150 dec	$C_{14}H_{18}ClN_3OS_2$ (343.9)	48.89 48.63	5.28 5.32	12.22 12.04	18.65 18.69 [d]	–	–	247 (4.32), 280 (4.36), sh 317 (3.88), 427 (3.93) [c]
3b	53	>110 dec	$C_{14}H_{20}ClN_3S_2$ (329.9)	50.96 50.49	6.11 5.94	12.74 12.42	19.44 19.64 [e]	–	–	246 (4.37), 279 (4.38), sh 316 (3.94), 427 (3.99) [c]
3c	81	>113 dec	$C_{12}H_{16}ClN_3OS_2$ •H_2O (335.9)	42.91 42.49	5.40 5.89	12.51 12.20	19.09 19.64 [f]	–	–	247 (4.31), 279 (4.35), sh 315 (3.92), 425 (3.92) [c]
4a	79	169-170 (ethyl acetate)	$C_{16}H_{19}N_3O_2S_2$ (349.5)	54.99 54.71	5.48 5.73	12.02 11.75	18.35 18.14	1630	–	240 (4.56), 299 (4.76), 431 (4.21)
4b	89	126-126.5 (ethyl acetate)	$C_{16}H_{21}N_3OS_2$ (335.5)	57.28 57.09	6.31 6.38	12.53 12.46	19.11 18.86	1620	–	236 (4.27), 298 (4.46), 437 (3.92)
4c	87	155-156 (ethyl acetate)	$C_{14}H_{17}N_3O_2S_2$ (323.4)	51.99 52.07	5.30 5.66	12.99 12.99	19.83 20.57	1625	–	238 (4.24), 298 (4.38), 429 (3.84)
5a	89	124-125 (cyclohexane)	$C_{17}H_{21}N_3O_2S_2$ (363.5)	56.17 56.40	5.82 5.87	11.56 11.44	17.64 17.23	1630	–	240 (4.37), 298 (4.52), 427 (4.00)
5b	76	90.5-91.5 (*n*-hexane)	$C_{17}H_{23}N_3OS_2$ (349.5)	58.42 58.64	6.63 7.02	12.02 11.99	18.35 18.49	1640	–	236 (4.29), 298 (4.46), 435 (3.95)
5c	71	121-123 (ethyl acetate)	$C_{15}H_{19}N_3O_2S_2$ (337.5)	53.39 52.95	5.68 5.79	12.45 11.93	19.00 18.58	1640	–	237 (4.25), 298 (4.37), 429 (3.84)
6a [g]	75	227-228 (propan-1-ol)	227-228 [3]					1660	–	
6b	81	144-145 (ethanol)	139-140 [3]					1650	–	
6c	65	234-235, conversion 210-220 (ethanol/methylene glycol)	238-239, conversion 220-227 [3]					1660	–	

[a] MS (70 eV): m/z (%) = 307 [M$^+$ (2a-H_2SO_4), 100]. [b] MS (70 eV): m/z (%) = 281 [M$^+$ (2c-H_2SO_4), 100]. [c] Dissolved in aqueous ethanolic hydrogen chloride (0.1 mole/l; 90% ethanol). [d] Cl (Calcd./Found): 10.31/10.77. [e] Cl: 10.75/11.32. [f] Cl: 10.56/11.22. [g] The uv data of **6a-c** are given in [3].

Table 2

MS (70 eV)-Fragmentation of 4-Acylimino-2-aminothieno[2,3-*d*][1,3]thiazines 4, 5: m/z (%)

Compound	M^+	$(M-R^5)^+$	$(M - CH_2CO)^+$ [a] $(M - C_2H_4CO)^+$ [b]	$(M - CH_2CO - SH)^+$ [a] $(M - C_2H_4CO - SH)^+$ [b]	$R^3R^4N-C{\equiv}S^+$	$R^3R^4N^+$	$R^5C{\equiv}O^+$
4a	349 (13)	334 (1)	307 (8) [c]	274 (2)	130 (100)	86 (49)	43 (34)
4b	335 (6)	320 (1)	293 (2) [c]	260 (1)	116 (100)	72 (13)	43 (34)
4c	323 (16)	308 (1)	281 (10) [c]	248 (3)	130 (100)	86 (58)	43 (61)
5a	363 (11)	334 (2)	307 (2) [c]	274 (2)	130 (100)	86 (59)	57 (35)
5b	349 (16)	320 (4)	293 (16) [c]	260 (5)	116 (100)	72 (16)	57 (35)
5c	337 (9)	308 (2)	281 (11) [c]	248 (3)	130 (100)	86 (43)	57 (39)

[a] Fragmentation of 4a-c. [b] Fragmentation of 5a-c. [c] Confirmed by metastable peaks.

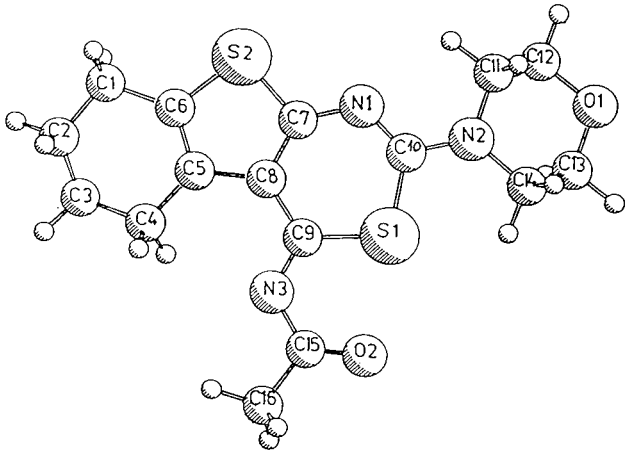


Figure. Molecular structure of compound 4a with the numbering scheme.

Table 3

Selected Bond Lengths (Å) and Bond Angles (°) of Compounds 4a

S(1)	-C(9)	1.775(3)		S(1)	-C(10)	1.769(3)	
O(2)	-C(15)	1.219(5)		N(1)	-C(7)	1.344(4)	
N(1)	-C(10)	1.309(4)		N(3)	-C(10)	1.340(4)	
N(3)	-C(9)	1.313(4)		N(3)	-C(15)	1.377(4)	
C(7)	-C(8)	1.404(4)		C(8)	-C(9)	1.404(4)	
C(15)	-C(16)	1.506(5)					
C(9)	-S(1)	-C(10)	103.6(1)	C(7)	-N(1)	-C(10)	119.4(2)
C(9)	-N(3)	-C(15)	121.0(2)	S(2)	-C(7)	-N(1)	117.8(2)
S(2)	-C(7)	-C(8)	110.7(2)	N(1)	-C(7)	-C(8)	131.5(2)
C(5)	-C(8)	-C(7)	112.5(2)	C(5)	-C(8)	-C(9)	126.9(2)
C(7)	-C(8)	-C(9)	120.5(2)	S(1)	-C(9)	-N(3)	121.4(2)
S(1)	-C(9)	-C(8)	118.8(2)	N(3)	-C(9)	-C(8)	119.8(2)
S(1)	-C(10)	-N(1)	126.0(2)	S(1)	-C(10)	-N(2)	114.5(2)
N(1)	-C(10)	-N(2)	119.5(2)	O(2)	-C(15)	-N(3)	114.4(3)
O(2)	-C(15)	-C(16)	121.0(3)	N(3)	-C(15)	-C(16)	124.7(3)

In order to prepare stable thiazine derivatives we had to prevent the regression of cyano group by replacing the 4-imino hydrogen of thiazines **2** by another rest. With the aim of preparing 4-acyliminothiazine derivatives we used acetic anhydride or propionic anhydride, respectively, as acylating agents. In fact, conversion of thioureas **1** into 4-acylimino-2-aminothienothiazines **4** and **5**, respectively, can be accomplished simple upon treatment of thioureas **1** with a mixture of the anhydride and concentrated sulfuric acid at room temperature. This new and convenient method affords the title compounds **4a-c**, **5a-c** in good yields.

Refluxing of thioureas **1** in concentrated hydrochloric acid affords the thienothiazin-4-ones **6a-c**, which were confirmed to be identical with the products we obtained earlier from the corresponding esters [3].

It is noteworthy that, under conditions used for the synthesis of **2-6** or for the ring cleavage of **2** and **3** the formation of Dimroth rearrangement products of 4-imino-1,3-thiazines, corresponding 4-thioxopyrimidines [8], could not be observed.

The structural elucidations of the new compounds **1c**, **2-5** were accomplished on the basis of ir, uv and microanalysis as well as mass spectra (Table 1 and 2). In order to establish unequivocally the structure of acyliminothiazines **4**, **5** and to assign the configuration of $=NC(=O)R^5$-side chain relative to the thiazine-skeleton, a representative product, **4a**, was subjected to a single crystal X-ray analysis [14]. The structure was solved using the programm SHELXS [16] by direct methods. The positions of the hydrogen atoms were calculated. The anisotropic refinement led to agreement factors R = 0.077, R_w = 0.086. A molecular plot of **4a** is shown (Figure), selected bond lengths and angles are given in Table 3 [17]. In solid state compound **4a** exist in *Z*-configuration around the C(9)=N(3) and *S-cis* conformation around the N(3)–C(15) bonds. The nonbonded intramolecular distance between S(1) and O(2) being 2.578(3) Å can be explained by assumption of polar interactions between the O and S atoms and described with the valence structures shown in Scheme 2 [18]. The atoms S(1), C(9), N(3), C(15) and O(2) form exactly a plane; deviation from this plane is maximum 0.06 Å.

EXPERIMENTAL

4,5-Dimethyl-2-isothiocyanatothiophene-3-carbonitrile (mp 76-76.5° from *n*-hexane) was obtained in 45% yield analogous to the literature procedure reported for the preparation of 2-isothio-

cyanato-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carbonitrile [19]. 4,5-Dimethyl-2-morpholinothiocarbonylaminothiophene-3-carbonitrile (**1c**) was prepared from 4,5-dimethyl-2-isothiocyanatothiophene-3-carbonitrile and morpholine according to [19].

2-Amino-4-iminothieno[2,3-*d*][1,3]thiazinium Hydrogen Sulfates **2a-c**. General Procedure.

To a solution of thiourea **1** (2 mmoles) and anhydrous acetonitrile (18 ml) concentrated sulfuric acid (0.25 ml) is added. The mixture is kept at room temperature for 4 days. The precipitate formed is collected by suction and dried under vacuum over potassium hydroxide, concentrated sulfuric acid.

2-Amino-4-iminothieno[2,3-*d*][1,3]thiazinium Chlorides **3a-c**. General Procedure.

To a suspension of thiourea **1** (2 mmoles) in anhydrous methanol methanolic hydrochloric acid is added until *p*H 2 is obtained. After 5 minutes the resultant solution is filtered and diethyl ether is added to the filtrate. The mixture is left for 24 hours at room temperature. The precipitate formed is collected by suction and dried under vacuum over potassium hydroxide, concentrated sulfuric acid.

4-Acetylimino-2-aminothieno[2,3-*d*][1,3]thiazines **4a-c**, 2-Amino-4-propionyliminothieno[2,3-*d*][1,3]thiazines **5a-c**. General Procedure.

Thiourea **1** (4 mmoles) is treated with a cooled mixture prepared from acetic anhydride, propionic anhydride, respectively, (8 ml) and concentrated sulfuric acid (1 ml) and kept at room temperature for 4 days. The resultant solution is poured into ice-water (400 ml). The product is collected by suction, dried and recrystallized from solvent given in Table 1.

2-Aminothieno[2,3-*d*][1,3]thiazin-4-ones **6a-c**. General Procedure.

A solution of thiourea **1** (2 mmoles) and concentrated hydrochloric acid (15 ml) is refluxed for 15 minutes. The mixture is brought to room temperature and water (30 ml) is added. The precipitate is separated by suction, washed with water (40 ml), dried and recrystallized from solvent given in Table 1. Compounds **6a-c** proved to be identical (ir, tlc) with the products which afford treatment of corresponding ethyl 2-thioureidothiophen-3-carboxylates with concentrated sulfuric acid [3].

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