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SYNTHESIS OF NOVEL N-AROYL- AND N-ARYLSULFONYLISOTHIAZOLE-2-IMINES BY CYCLIZATION OF THIOCYANATOVINYLALDEHYDE HYDRAZONES

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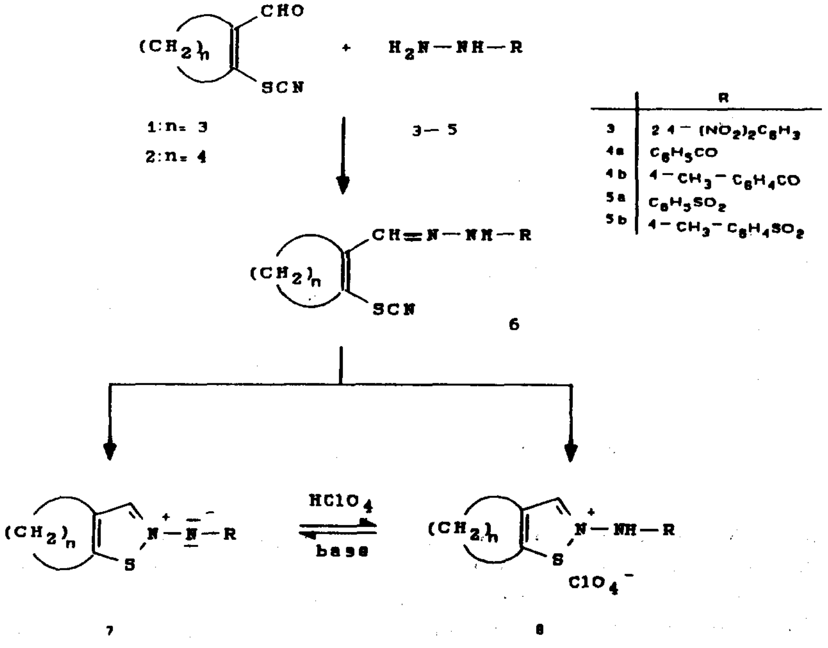
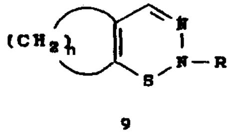
Summary: The synthesis of N-aroyl- and N-arylsulfonylisothiazole-2-imines **7c-f** as well as the corresponding acceptor-substituted 2-aminoisothiazolium salts **8c-f** by cyclocondensation of thiocyanatovinylaldehyde hydrazones **6c-f** is reported. The alternative cyclization route to 1,2,3-thiadiazines is not observed.

We have recently demonstrated the use of thiocyanatovinylaldehydes **1**, **2** as versatile, C_3S building blocks in the synthesis of organic compounds. One application involved the transformation with N-nucleophiles such as ammonia and amines to isothiazoles[1] and isothiazolium salts[2]. Now we report on the reactions of thiocyanates **1**, **2** with acceptor-substituted hydrazines **4** and **5**.



	R
3	2 4 − $(NO_2)_2C_6H_3$
4a	C_6H_5CO
4b	4 − CH_3 − C_6H_4CO
5a	$C_6H_5SO_2$
5b	4 − CH_3 − $C_6H_4SO_2$

6,7,8,9	n	R
a	3	C_6H_5CO
b	3	$C_6H_5SO_2$
c	4	C_6H_5CO
d	4	4 − CH_3 − C_6H_4CO
e	4	$C_6H_5SO_2$
f	4	4 − CH_3 − $C_6H_4SO_2$



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Some years ago Entenmann reported that 2-thiocyanatocycloalken-1-carbaldehydes, such as **2** react with 2,4-dinitrophenyl hydrazine **3** to give 1,2,3-thiadiazine **9**.[3] The structure of this compound was determined only by ^{1}H-NMR- and mass-spectroscopy[4]. The 1,2,3-thiadiazine ring is not often cited. References exist only when the 1,2,3-thiadiazine is annellated with a naphthalene ring and this compound is instable[5]. Furthermore, a few stable 2H-1,2,3-benzothiadiazine-1,1-dioxides[6-8] and dihydro derivatives[9] were reported.

We have investigated the reactions of 2-thiocyanatocyclohexene-1-carbaldehyde **2** with substituted hydrazines, such as benzhydrazides **4a,b** in aqueous ethanolic solution at room temperature for 1 hour. We found two products, **6c,d** and compounds without SCN-group (identified by IR spectra). It is not possible to obtain **6c,d** as pure compounds. During the purification process a significant loss of **6** has been observed with concomitant formation of other substances with possible structures of **7** and **9**. These compounds were identified as N-aroylisothiazol-2-imines **7c,d** by spectroscopic methods[10]. In particular, the IR spectrum of the compounds **7** shows a carbonyl absorption bond around 1600 cm-1. This low frequency is always found in the IR spectra of heteroaromatic N-acylimines, opposite to the benzoylamino group (1690 cm^{-1}) in the salts **8c,d**. The hydrazones **6c,d** react with 70% perchloric acid at 0°C to give isothiazolium salts **8c,d**[11]. There exists an equilibrium between **7** and **8**.

Further we have investigated the reaction of thiocyanate **2** with benzenesulfonyl hydrazides **5a,b**. The hydrazones **6e,f** are stable enough to be isolated (Table 1) and their structures were characterized by spectroscopic methods[12]. The treatment of **6e,f** with 70% perchloric acid at 0°C led to colourless crystalline isothiazolium salts **8e,f** as primary cyclic products after a short time. The compounds **8e,f** react easily with bases e.g. dicyclohexylamine to N-arylsulfonylisothiazole-2-imines **7e,f**[13]. The formation of 1,2,3-thiadiazines **9** is not observed.

Table 1 Selected data of 6, 7 and 8

compounds		6		7		8	
	n	yield [%]	mp^a [°C]	yield [%]	mp^a [°C]	yield [%]	mp^b [°C]
a	3	95	158-160				
b	3	85	127-131				
c	4			96	225-227	45	170-171
d	4			79	228-230	55	159-161
e	4	80	121-124	75	153-156	75	173-176
f	4	64	123-126	85	162-165	90	174-177

a) Recrystallisation from ethanol, b) from acetic acid.

The structure of **7d** as a five (not six) membered heterocyclic ring system has been confirmed unequivocally by an X-ray structure analysis (Fig. 1)[14]. The bond lengths C10 - C15 (1.377), S1 -C15 (1.702), N2 - C9 (1.331), N1 - C8 (1.330) and N1 - N2 (1.383), lie between those of C/C, S/C, N/C and N/N single and double bonds and indicate electron delocalization in the heteroaromatic ring with the participation of the acylimino group. Compound **7d** exhibits a short non-bonded intramolecular S...O=C 1,5 interaction (2.537(2) Å). The S...O distance falls in the middle of the critical region (2 - 3 Å)[15].

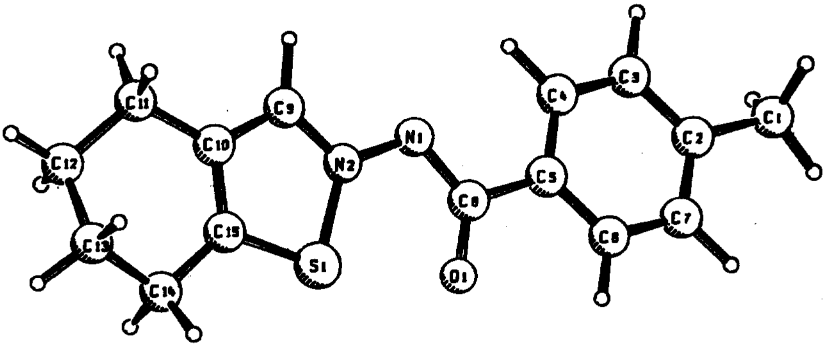


Fig. 1 Crystal structure of the N-aroylisothiazole-2-imine **7d**. Selected bond lengths [Å] and bond angles [°].

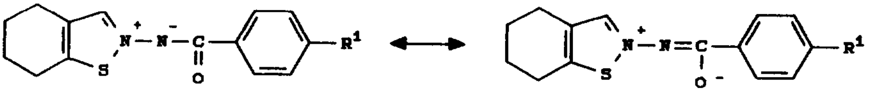
Bond lengths

S1 - C15	1.702 (2)	C8 - O1	1.258 (3)	C10 - C15	1.377 (3)
S1 - N2	1.725 (2)	C8 - C5	1.494 (3)	C14 - C15	1.509 (3)
N2 - N1	1.383 (2)	C5 - C6	1.390 (3)	C10 - C11	1.503 (2)
N1 - C8	1.330 (3)	C9 - C10	1.405 (3)	N2 - C9	1.331 (3)

Bond angles

C15 - S1 - N2	90.4(1)	O1 - C8 - C5	119.9(2)	C9 - C10 - C11	127.0(2)
S1 - N2 - N1	126.4(2)	C8 - C5 - C6	118.7(2)	C10 - C11 - C12	110.7(2)
N2 - N1 - C8	113.2(2)	S1 - N2 - C9	112.2(2)	C9 - C10 - C15	110.7(2)
N1 - C8 - O1	125.0(2)	N1 - N2 - C9	121.4(2)	C15 - C10 - C11	122.3(2)
N1 - C8 - C5	115.1(2)	N2 - C9 - C10	113.9(2)	C10 - C15 - S1	112.8(2)

Thiocyanate **1** reacts with hydrazines **4** and **5** to give stable hydrazones **6a,b**, which cannot be cyclized further. The stability of compounds **6** depends upon the nucleophilicity of the nitrogen atom of the azomethine group which is influenced by the substituent R and on the electrophilicity of the sulfur atom of the thiocyanate group. In the case of the N-aroylimines **7c,d** the stabilization of the negative charge by the π-acceptor effect of the carbonyl group favours the cyclization.



7c,d

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10. **7d**: IR (KBr): ν=1590 (CO), 1525, 1460, 1360 cm^{-1}; ^{1}H-NMR (100 MHz, CDCl$_3$): δ=8.54 (s, 1H, CH=), 8.02, 7.21 (2d, 4H, J=8.23 Hz), 2.82 (m, 2H, -CH$_2$-C=), 2.67 (m, 2H, -CH$_2$-C=), 2.38 (s, 3H, CH$_3$), 1.90 (m, 4H, - (CH$_2$)$_2$-); MS (70 eV): m/z=272 (38, M$^+$), 211(6), 119(100), 91(23).
11. **8d**: IR (KBr): ν=3120 (NH), 1690 (CO), 1610, 1460, 1270 cm^{-1}; ^{1}H-NMR (100 MHz,CDCl$_3$): δ=9.00 (s, 1H, CH=), 7.86, 7.25 (2d, 4H, J=7.95 Hz), 2.90 (m, 2H, -CH$_2$-C=), 2.63 (m, 2H, -CH$_2$-C=), 2.34 (s, 3H, CH$_3$), 1.88 (m, 4H, -(CH$_2$)$_2$-); MS (70 eV): m/z=272 (45, M$^+$-HClO$_4$).
12. **6e**: IR (KBr): ν=3140 (NH), 2170 (SCN), 1320, 1160 (SO$_2$) cm^{-1}; ^{1}H-NMR (100 MHz, CDCl$_3$): δ=10.93(s, 1H, NH), 7.89(s, 1H, CH=), 7.85, 7.43 (2m, 5H, arom.), 2.46 (m, 2H, -CH$_2$-C=), 2.26 (m, 2H, -CH$_2$-C=), 1.59 (m, 4H, -(CH$_2$)$_2$-); MS (70 eV): m/z=321 (1, M$^+$), 296 (1, M$^+$-HCN), 262 (1, M$^+$-HSCN), 157(57), 153(100), 125(16), 111(16), 77(69), 51(31).
13. **7e**: IR (KBr): ν=1280, 1125 (SO$_2$) cm^{-1}; ^{1}H-NMR (100 MHz, CDCl$_3$): δ=7.95 (s, 1H, CH=), 7.71, 7.36 (2m, 5H, arom.), 2.75 (m, 2H, -CH$_2$-C=), 2.53 (m, 2H,-CH$_2$-C=), 1.78 (m, 4H, -(CH$_2$)$_2$-); MS (70 eV): m/z=294.4 (1, M$^+$), 262(1), 198(1), 157(13), 153(19), 111(12), 93(19), 77(100).
14. $C_{15}H_{16}N_2OS$. M=272.4, colourless prisma, size 0.1*0.5*0.6 mm, a=6.3836(6), b=7.3235(8), c=15.535(2)Å, α=84.339(7), ß=84.213(7), γ=70.597(6), V=679.9 Å^3, Z=2, space group triclin P1, absorption coefficient m=2.3 cm^{-1}. The measurements were performed with Stoe Stadi 4; radiation MoK$_\alpha$; unique reflections 2331, observed 2183 with $F > 3\sigma(F)$, 3° < 2Θ < 50°; structure solution direct methods (SHELX -86) refinement (SHELX-76) converged at R=0.043 and R$_w$=0.042. Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D W-7544 Eggenstein-Leopoldshafen 2 on quoting the depository number CSD-400033; the names of the authors, and the journal citation.
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