Formylation Products of Thioamides; VII[1]. Synthesis of New *N*-(3-Aminothioacryloyl)-formamidines and *N,N'*-Bis[aminomethylidene]thioureas by Bis-iminoformylation of Thioacetamides and Thiourea with Formamide Acetals

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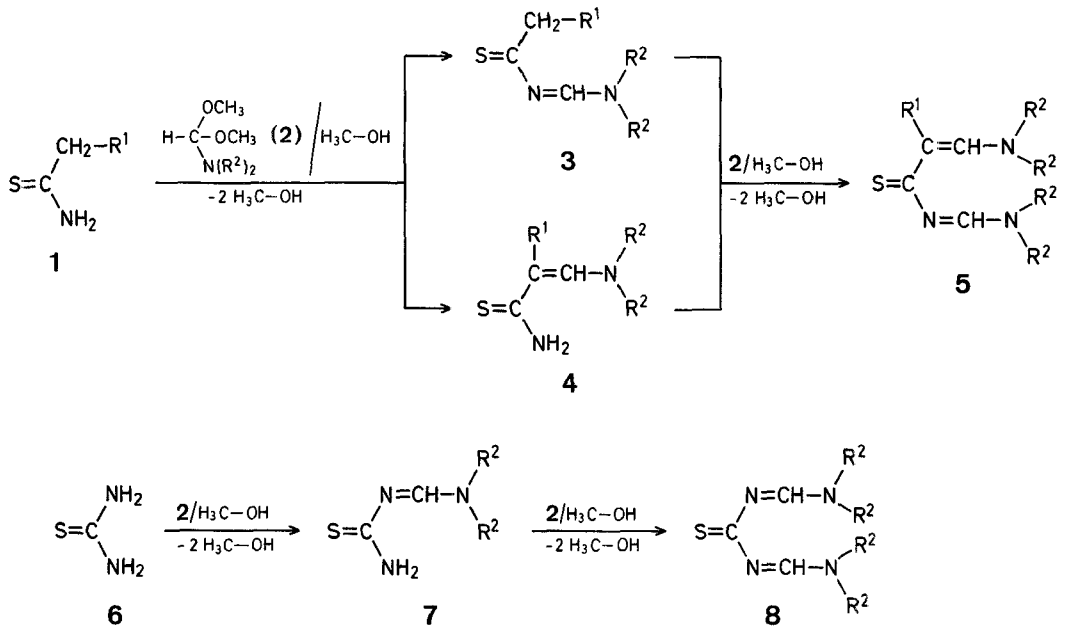
Aminothiocarbonyl compounds such as *N*-unsubstituted thioamides[2-7] or thioureas[7-12] are usually attacked by iminoformylating reagents, e.g. formamide chlorides or acetals **2**, at the nucleophilic amino group. In this way *N*-thiocarbonyl-formamidines are obtained. On the other hand, *C*-iminoformylation at the nucleophilic methylene group takes place when formamide chlorides[13] or formaminal esters[14] react with *N,N*-disubstituted thioacetamides, giving rise to the formation of 3-aminothioacrylamides.

N-Unsubstituted thioacetamides **1** or thiourea (**6**) possess two nucleophilic positions susceptible to electrophilic attack. Therefore, by analogy with the known reactions of acetam-

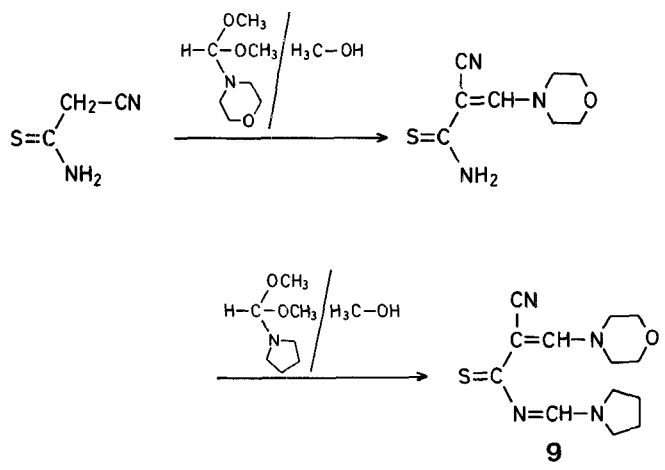


ide[14] or urea[15] with formamide acetals **2** or formaminal esters, the thiocarbonyl compounds **1** and **6** can be assumed to react twice with an excess of formamide derivatives. As a result, novel *N*-(3-aminothioacryloyl)-formamidines **5** and *N,N'*-bis[aminomethylidene]thioureas **8** would be formed via intermediate thiocarbonyl amidines **3**[6] or **7**[8] and 3-aminothioacrylamides **4**[16]. Compounds of these types are known in a few cases.

Formaminal esters are reported[14] to be not useful in a possible bis-iminoformylation of **1** or **6**. Our investigations with formamide chlorides have led to the same conclusion.

However, the synthesis of **5** or **8** can be achieved without difficulties when thioacetamides **1** or thiourea (**6**) are reacted with an excess of formamide acetals **2**[17]. To obtain good yields it is necessary to use three equivalents of **2** (Method A).

The application of two equivalents of reagent **2** leads to mixtures of products containing only small amounts of *N*-(3-aminothioacryloyl)-formamidines **5** and/or *N,N'*-bis[aminomethylidene]thioureas **8**, respectively. Under these conditions the main products of the reaction of compounds **1** are *N*-thioacylformamidines **3** or 3-aminothioacrylamides **4**, whereas reaction of **6** yields *N*-aminomethylidene-thioureas **7** (see Table).



The monoiminoformylation products **3**, **4**, and **7** (except **4c**) can be transformed to the corresponding products **5** or **8** by subsequent treatment with formamide acetals **2** (Method B). In this way also, *N*-(3-aminothioacryloyl)-formamidines possessing different aminomethylene groups like, for example, compound **9** (see Table) can be prepared. The stepwise synthesis (Method B) of the bis-iminoformylation products **5** or **8** and examination of the reaction progress in Method A by thin-layer chromatography provides proof for the intermediacy of **3**, **4**, and **7**, respectively. Depending on the nature of the substituent R^1, in the reaction of the thioacetamides **1** with **2** either **3** (e.g. $R^1 = C_6H_5$) or **4** (e.g. $R^1 = H$, CN) are formed as intermediates.

The *N*-(3-aminothioacryloyl)-formamidines **5** and **9**, and the *N,N'*-bis[aminomethylidene]thioureas **8** (see Table) are stable yellow to orange coloured compounds. Their structures are confirmed by spectroscopic data and by microanalyses. It should be mentioned, however, that the compounds **8** loose one aminomethylene group, giving rise to the formation of **7**, when recrystallised from alcohols.

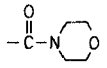
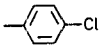
***N,N*-Tetramethylene-*N'*-phenylthioacetyl-formamidine Hydroperchlorate (3a · $HClO_4$), 3-Amino-thioacrylamides 4, and *N*-Aminothiocarbonyl-*N',N'*-(3-oxapentamethylene)-formamide (7a); General Procedure:**
A mixture of substituted thioacetamide **1** (0.01 mol), or thiourea (**6**; 0.76 g, 0.01 mol), methanol (10 ml), and substituted formamide dimethylacetal **2** (0.02 mol) is refluxed for 10 min. After cooling to room temperature the products **4** or **7a** precipitate and are filtered by suction and recrystallised. Compound **3a** is precipitated as its hydroperchlorate by the addition of 70% perchloric acid (1 ml) to the cold reaction mixture.

***N*-(3-Aminothioacryloyl)-formamidines 5, *N,N'*-Bis[aminomethylidene]thioureas 8, and *N*-(2-Cyano-3-morpholinothioacryloyl)-*N',N'*-tetramethyleneformamidine (9); General Procedure:**

Method A: A mixture of substituted thioacetamide **1** (0.01 mol) or thiourea (**6**; 0.76 g, 0.01 mol), methanol (10 ml), and substituted formamide dimethylacetal **2** (0.03 mol) is refluxed for 15 min (when **1** is used) or 30 min (when **6** is used). The resulting mixture is allowed to cool to room temperature. The precipitation of the product may be completed by the evaporation of some solvent. The product is filtered by suction and recrystallised.

Method B: A mixture of *N*-thioacyl-formamidine **3** (0.01 mol) or *N*-aminomethylidene-thiourea **7** (0.01 mol) or substituted 3-aminothio-

Table. Compounds **3a**, **4a–c**, **5a–e**, **7a**, **8a**, **b**, and **9** prepared

Product No.	R^1	R^2	R^3	Yield [%] (Method)	m.p. [°C] (solvent)	Molecular Formula[a]	^{1}H-N.M.R. (solvent) δ [ppm]
3a · $HClO_4$		$-(CH_2)_4-$		51[b]	159–161° (AcOH)	$C_{13}H_{17}ClN_2O_4S$ (332.8)	*(F_3C—COOH): 1.75 (m, 4H); 3.30* (m, 2H); 3.61 (m, 2H); 3.83 (s, 2H); 6.86 (s, 5H_{arom}); 8.78 (s, 1H)
4a	H	$-(CH_2)_4-$		33	212–213° (AcOH)	$C_7H_{12}N_3S$ (156.3)	($CDCl_3$/DMSO-d_6): 1.85 (m, 4H); 3.21 (m, 4H); 5.14 (d, 1H, J = 11 Hz); 7.38 (br, 2H); 7.93 (d, 1H, J = 11 Hz)
4b	$-CN$	$-(CH_2)_2-O-(CH_2)_2-$		96[c]	229–231° (dec) (AcOH)	$C_8H_{11}N_3OS$ (197.3)	(DMSO-d_6): 3.61 (m, 8H); 7.88 (s, 1H); 8.26 (s, 1H); 8.65 (s, 1H)
4c		$-(CH_2)_2-O-(CH_2)_2-$		60	181–183° (CH_3OH)	$C_{12}H_{19}N_3O_3S$ (285.4)	*($CDCl_3$): 3.50 (m, 16H); 7.08 (s,* 2H); 8.09 (s, 1H)
5a · $HClO_4$	H	CH_3	CH_3	21[d] (A)	200–203° (CH_3OH)	$C_8H_{16}ClN_3O_4S$ (255.8)	(DMSO-d_6): 2.98 (s, 3H); 3.20 (s, 3H); 3.26 (s, 3H); 3.38 (s, 3H); 6.08 (d, 1H, J = 12 Hz); 8.31 (d, 1H, J = 12 Hz); 9.21 (s, 1H)
5b	$-CN$	$-(CH_2)_2-O-(CH_2)_2-$		98 (A)	202–203° (acetone)	$C_{13}H_{18}N_4O_2S$ (294.4)	($CDCl_3$): 3.78 (m, 16H); 8.63 (s, 1H); 8.78 (s, 1H)
5c		$-(CH_2)_2-O-(CH_2)_2-$		86 (A)	180–182° (CH_3OH)	$C_{18}H_{23}N_3O_2S$ (345.5)	($CDCl_3$): 3.00 (m, 4H); 3.40 (m, *12H); 7.15 (m, 5H); 8.43 (s, 1H);* 8.53 (s, 1H)
5d		$-(CH_2)_4-$		90 (A); 93 (B)	162–163° (CH_3OH)	$C_{18}H_{23}N_3S$ (313.5)	(CD_3CN): 2.00 (m, 8H); 3.41 (m, 8H); 7.31 (m, 5H); 9.13 (s, 2H)
5e		$-(CH_2)_2-O-(CH_2)_2-$		53 (A)	186–188° (CH_3OH)	$C_{18}H_{22}ClN_3O_2S$ (379.9)	—
7a	–	$-(CH_2)_2-O-(CH_2)_2-$		98	191–192° (CH_3CN)	$C_6H_{11}N_3OS$ (173.3)	(DMSO-d_6): 3.50 (m, 8H); 7.80 (s, 1H); 8.10 (br, 1H); 8.55 (s, 1H)
8a	–	$-(CH_2)_2-O-(CH_2)_2-$		96 (A); 98 (B)	216–217° (CH_3CN)	$C_{11}H_{18}N_4O_2S$ (270.4)	($CDCl_3$): 3.56 (m, 16H); 8.85 (s, 2H)
8b	–	$-(CH_2)_4-$		96 (A)	142–144° (acetone)	$C_{11}H_{18}N_4S$ (238.4)	($CDCl_3$): 1.84 (m, 8H); 3.51 (m, 8H); 8.96 (s, 2H)
9	–	–		56 (B)	170–171° (CH_3OH)	$C_{13}H_{18}N_4OS$ (278.4)	($CDCl_3$): 1.93 (m, 8H); 3.68 (m, 8H); 8.75 (s, 1H); 8.88 (s, 1H)

[a] Satisfactory microanalyses obtained: C ±0.39, H ±0.31, N ±0.38, S ±0.44; exceptions: **3a** · $HClO_4$, C −0.52, **5a**, C −0.42.
[b] Product **3a** is also obtained in 50% yield using the corresponding formamide chloride by the procedure of Ref.[6].
[c] The preparation is also possible without heating.
[d] Reflux time: 1.5 h.

acrylamide **4** (0.01 mol), methanol (10 ml), and substituted formamide dimethylacetal **2** (0.02 mol) is refluxed for 15 min. The products are isolated as described for Method A.

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