Formylation Products of Thioamides; Part 12[1]. Synthesis of Thiazoles by the Reaction of S-Alkylated Thioamides or Thioureas with Acid Derivatives

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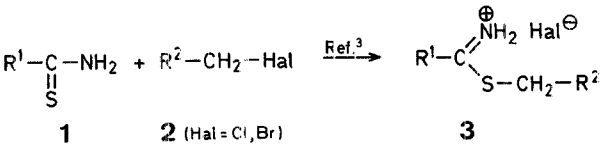
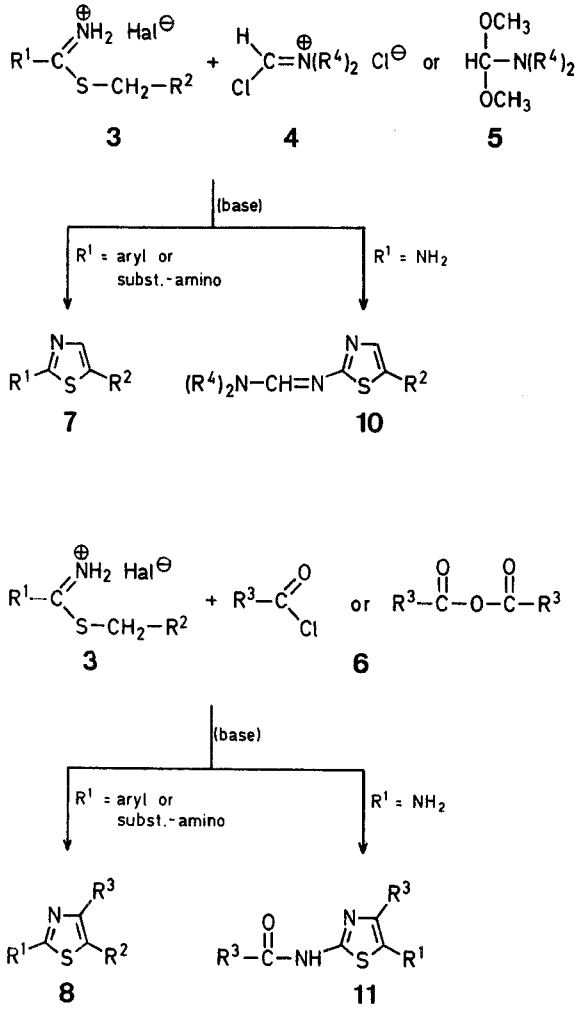
Isothiuronium salts **3** ($R^1 = NH_2$) are reported[2] to react with formamide chlorides **4** to give either 3-alkylmercapto-2,4-diazapentamethinium salts (if R^2 = H or alkyl) by bis-iminoformylation or 3-chloro-2,4-diazapentamethinium salts (if R^1 = benzyl) by bis-iminoformylation and substitution of the alkylmercapto group by chlorine. We now report on a third type of products, thiazoles, formed from the reactands **3** ($R^1 = NH_2$) or related benzylmercaptomethyleniminium salts **3** (R^1 = aryl or substituted amino), conveniently prepared[3] by alkylation of the corresponding thioamide compounds **1**, and formamide chlorides **4** or other acid derivatives, such as substituted formamide acetals **5**, acyl chlorides or anhydrides **6**.



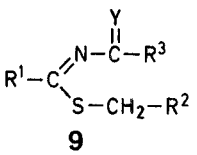
1 **2** (Hal = Cl, Br) **3**

The reaction of mercaptomethyleniminium salts **3** (R^1 = aryl or substituted amino) possessing electron-withdrawing aryl substituents R^2 with formamide chlorides **4** or acetals **5** in the presence of a base, gives rise to the formation of 2,5-disubstituted thiazoles **7** (Table 1). If other acid derivatives **6** instead of the **4** or **5** are employed in this reaction, 2,4,5-trisubstituted thiazoles **8** (Table 1) are obtained.



3 4 5 7 10 3 6 8 11

In the case of the reaction of compound **3** [R^1 = 4-$(H_3C)_2N$—C_6H_4, R^2 = 4-O_2N—C_6H_4, Hal = Br] with acetic anhydride it was possible to isolate a corresponding *N*-acylthioimidate **9** (Y = O, R^3 = CH_3) (Table 1, compound **9a**) which could be cyclised by subsequent treatment with sodium ethoxide to thiazole **8b**.



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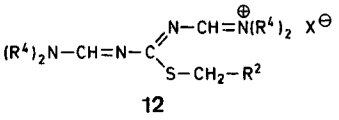
This result allows us to interpret the formation of the thiazoles **7** and **8** in the following manner. In the first step, the corresponding acid derivative **4**, **5**, or **6** attacks the N-atom of the reactand **3**. The methylene group of the resulting *N*-iminoformyl **9** [Y = $^{\oplus}N(R^4)_2$; R^3 = H] or *N*-acylthioimidate **9** (Y = O) is deprotonated by the base and subsequently interacts with the R^3-substituted C-atom while condensation and cyclisation takes place.

In a similar way, but by twofold iminoformylation or acylation, *N*-unsubstituted isothiuronium salts **3** (R^1 = NH_2) react with acid derivatives **4**,**5**, or **6** in the presence of a base. Hence, the amino group of the **3** which remains exocyclic, is found in the thiazoles **10** or **11** (see Table 2) to be functionalised, that is as a formamidino or acylamino substituent, respectively. The isolation of the substituted 3-benzylmercapto-2,4-diazapentamethinium salt **12a** (Table 2) and its cyclisation to the corresponding 2-formamidinothiazole **10a** shows that both amino groups of the reactand **3** (R^1 = NH_2) have been iminoformylated or acylated before the cyclisation takes place.



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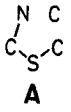
2,5-Disubstituted thiazoles **7** (R^1 = substituted amino)[4] or analogous 5-acyl substituted compounds (R^2 = acyl; R^1 = aryl or substituted amino)[5-8] can also be prepared by a reversed reaction sequence starting from the corresponding thioamides **1**, that is first by iminoformylation[7-11] and subsequently by alkylation[4-8]. We prepared compound **7c** following these known procedures[6] in order to obtain further proof for the structural assignment of **7**.

The synthesis of the thiazoles **7**, **8**, **10**, and **11** is the first example of the formation of an uncondensed thiazole system following the system **A**, which has been elaborated independently[12] of a recently reported[13] application of this synthetic principle in the preparation of an imidazothiazole. The advantage of the thiazole synthesis shown here is the easy variability of the substituent R^3. An independent synthesis of the formamidinothiazoles **10** will be reported soon[14].



A

The structures of all products **7**–**12** are confirmed by their spectroscopic data (Tables 1 and 2) and by microanalyses.

Thiazoles 7, 8, 10, and 11 and *N*-Acylthioimidate 9a; General Procedures:

Method A: A solution of formamide chloride **4** [prepared by dropwise addition of phosphoryl chloride (2.3 g, 15 mmol for preparation of **7** or 3.4 g, 22 mmol for preparation of **10**) to a substituted formamide H—CO—$N(R^4)_2$ (20 ml)], is combined with the corresponding thioimidate **3** (1 mmol). After the mixture has been heated at 80°C for 10 min, triethylamine (2 g, 20 mmol) is added. The heating is continued for further 10 min. After cooling to room temperature, solid products are filtered by suction, and washed with water. If no product precipitates, the reaction mixture is poured into water (50 ml). The thiazole is finally recrystallised from ethanol.

Method B: Triethylamine (3 g, 30 mmol) is added to a mixture of the thioimidate **3** (10 mmol), methanol (20 ml), and substituted formamide dimethyl acetal **5** (15 mmol for the synthesis of **7** or 30 mmol for the synthesis of **10**). The resulting solution is refluxed until the product precipitates. If thiazoles **10** are prepared, the reaction mixture is allowed to cool to room temperature after 30 min of reflux. The product is filtered by suction, washed with water, and recrystallised from ethanol.

Method C: A mixture of the thioimidate **3** (10 mmol), acetic anhydride (1.5 g, 15 mmol for the synthesis of **8** or 2.6 g, 25 mmol for the synthesis of **11**), and pyridine (20 ml) is refluxed for 15 min. If a thiazole **8** is prepared, triethylamine (3 g, 30 mmol) is added and the reflux is continued for further 10 min. The cold reaction mixture is poured into water (50 ml). After the product has solidified, it is filtered by suction, and recrystallised from ethanol.

Method D: A mixture of thioimidate **3** (10 mmol), acyl chloride **6** (25 mmol), and pyridine (20 ml) is refluxed for 15 min. The cold

Table 1. Thiazoles **7** and **8** and *N*-Acylthioimidate **9a** prepared

Substrate **3** R^1	R^2	Hal	Substrate **4**, **5**, or **6** R^3	R^4	R^4	Product	Yield [%] (Method)	m.p. [°C] (ethanol)	Molecular Formula[a]	I.R. (KBr) ν_{NO_2} [cm^{-1}]	^{1}H-N.M.R. ($CDCl_3$) δ [ppm]
4-$(H_3C)_2N$—C_6H_4	4-O_2N—C_6H_4	Br	–	CH_3	CH_3	**7a**	26 (A)	275–277°	$C_{17}H_{15}N_3O_2S$ (325.4)	1510, 1332	–
H_3C—NH—	4-O_2N—C_6H_4	Br	–	—$(CH_2)_2$—O—$(CH_2)_2$—		**7b**	75 (B)	269–271°	$C_{10}H_9N_3O_2S$ (235.3)	1530, 1330	–
C_6H_5—NH—	4-O_2N—C_6H_4	Br	–	—$(CH_2)_2$—O—$(CH_2)_2$—		**7c**[b]	84 (B)	254–255°	$C_{15}H_{11}N_3O_2S$ (297.3)	1512, 1340	–
C_6H_5—NH—	2,4-di-O_2N—C_6H_3	Cl	–	—$(CH_2)_5$—		**7d**	44 (A)	217–218°	$C_{15}H_{10}N_4O_4S$ (342.4)	1512, 1337	–
4-H_3CO—C_6H_4	4-O_2N—C_6H_4	Br	CH_3	–	–	**8a**[c]	43 (C)	171–172°	$C_{17}H_{14}N_2O_3S$ (326.4)	1515, 1335	2.46 (s, 3H); 3.74 (s, 3H); 6.81 (d, 2H, J = 9 Hz); 7.49 (d, 2H, J = 9 Hz); 7.45 (d, 2H, J = 9 Hz); 8.15 (d, 2H, J = 9 Hz)
4-$(H_3C)_2N$—C_6H_4	4-O_2N—C_6H_4	Br	CH_3	–	–	**8b**	41[d]	200–201°	$C_{18}H_{17}N_3O_2S$ (339.4)	1512, 1325	–
H_3C—NH—	4-O_2N—C_6H_4	Br	CH_3	–	–	**8c**	50 (C)	213–215°	$C_{11}H_{11}N_3O_2S$ (249.3)	1512, 1322	–
C_6H_5—N(CH_3)—	4-O_2N—C_6H_4	Br	CH_3	–	–	**8d**[e]	41 (C)	101–102°	$C_{17}H_{15}N_3O_2S$ (325.4)	1500, 1325	2.32 (s, 3H); 3.42 (s, 3H); 7.25–7.35 (m, 7H); 8.01 (d, 2H, J = 9 Hz)
4-$(H_3C)_2N$—C_6H_4	4-O_2N—C_6H_4	Br	CH_3	–	–	**9a**[f]	89 (C)	95–96°	$C_{18}H_{19}N_3O_3S$ (357.4)	1520, 1340; 1680 (C=O)	1.86 (s, 3H); 2.89 (s, 6H); 4.24 (s, 2H); 6.61 (d, 2H, J = 9 Hz); 7.29 (d, 2H, J = 9 Hz); 7.56 (d, 2H, J = 9 Hz); 7.85 (d, 2H, J = 9 Hz)[g]

[a] Satisfactory microanalyses obtained: C, ±0.39; H, ±0.20; N, ±0.46; S, ±0.31.

[b] Prepared independently from *N*-phenyl-*N'*-dimethylaminomethylidenethiourea and *p*-nitrobenzyl bromide; yield: 94%.

[c] U.V. (CH_3CN): λ_{max} (logε) = 221 (sh, 4.10); 252 (4.03); 310 (sh, 4.16); 367 nm (4.33).

[d] Prepared by treatment of **9a** with 2 equivalents of sodium ethoxide in ethanol.

[e] U.V. (CH_3CN): λ_{max} (logε) = 273 (4.03); 413 nm (4.18).

[f] Y = O; compound formed instead of the expected thiazole **8b**.
M.S.: m/e = 357 (M^+, 5%); 148 (12%); 147 (100%); 145 (9%).

[g] In DMSO-d_6.

Table 2. *N*-Functionalised 2-Aminothiazoles **10**, **11**, and 2,4-Diaza-3-(4-nitrobenzylmercapto)-tetramethylphentamethinium Perchlorate (**12a**) prepared

Substrate **3** R^2	(R^1 = NH_2) Hal	Substrate **4**, **5**, or **6** R^3	R^4	R^4	Product	Yield [%] (Method)	m.p. [°C] (ethanol)	Molecular Formula[a]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (solvent) δ [ppm]
4-O_2N—C_6H_4	Br	–	CH_3	CH_3	**10a**	41 (A); 74[b]	227–228°	$C_{12}H_{12}N_4O_2S$ (276.3)	–	–
4-O_2N—C_6H_4	Br	–	—$(CH_2)_4$—		**10b**	40 (B)	238–240°	$C_{14}H_{14}N_4O_2S$ (302.4)	–	–

4-O_2N—C_6H_4	Br	–	—$(CH_2)_2$—O—$(CH_2)_2$—	**10c**[e]	63 (B)	229–230°	$C_{14}H_{14}N_4O_3S$ (318.4)	–	(CF_3COOH): 2.91 (s, 3H); 3.01 (s, 3H); 7.28 (d, 2H, J = 9 Hz); 7.39 (s, 1H); 7.89 (s, 1H); 7.90 (d, 2H, J = 9 Hz)
4-O_2N—C_6H_4	Br	CH_3	–	**11a**[d]	76 (C)	266–268°	$C_{12}H_{11}N_3O_3S$ (277.3)	1660	(DMSO-d_6/$CDCl_3$): 2.07 (s, 3H); 2.35 (s, 3H); 7.50 (d, 2H, J = 9 Hz); 8.12 (d, 2H, J = 9 Hz); 12.05 (s, 1H)
2,4-di-O_2N—C_6H_3	Cl	CH_3	–	**11b**	84 (C)	200–202°	$C_{12}H_{10}N_4O_5S$ (322.3)	1690	–
4-O_2N—C_6H_4	Br	C_6H_5	–	**11c**[e]	54 (D)	180–182°	$C_{22}H_{15}N_3O_3S$ (401.4)	1695	–
2,4-di-O_2N—C_6H_3	Cl	C_6H_5	–	**11d**[f]	56 (D)	155–157°	$C_{22}H_{14}N_4O_5S$ (446.4)	1665	–
4-O_2N—C_6H_4	Br	–	CH_3	CH_3	**12a**	57 (A)[g]	138–140°[h]	$C_{14}H_{20}ClN_5O_6S$ (421.9)	–	(DMSO-d_6): 3.30 (s, 6H); 3.42 (s, 6H); 4.75 (s, 2H); 7.79 (d, 2H, J = 9 Hz); 8.30 (d, 2H, J = 9 Hz); 8.77 (s, 2H)

[a] Satisfactory microanalyses obtained: C, ± 0.42; H, ± 0.45; N, ± 0.47; S, ± 0.38; Cl, + 0.41.

[b] By short boiling of **12a** with triethylamine in ethanol.

[c] U.V. (CH_3CN): λ_{max} (log ε) = 236 (4.06); 312 (3.94); 404 nm (4.38).

[d] U.V. (CH_3CN): λ_{max} (log ε) = 260 (3.98); 362 nm (4.15).

[e] U.V. (CH_3CN): λ_{max} (log ε) = 237 (4.31); 265 (4.42); 305 (sh, 4.02); 368 nm (4.00).

[f] U.V. (CH_3CN): λ_{max} (log ε) = 242 (4.42); 267 (4.22); 380 nm (sh, 3.19).

[g] In the absence of triethylamine.

[h] Not recrystallized since cyclisation to **10a** occurs on heating.

reaction mixture is poured into water (50 ml). When the product has solidified, it is filtered by suction, and recrystallised from ethanol.

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