Reaction of Substituted Thioacetamides with Formamide Chlorides; A New Synthesis of 3-Amino- and 3-Hydroxypropenethioamides

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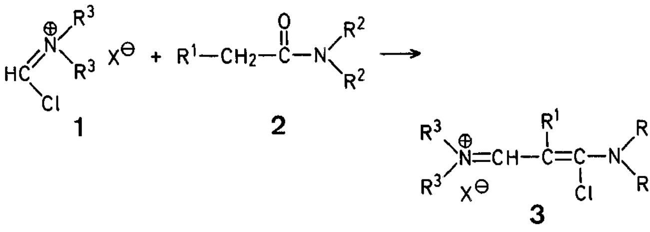
Formamide chlorides (**1**) are important synthetic intermediates; they undergo iminomethylation reactions with a variety of nucleophilic substrates[1]. The reactions of **1** with methylene ketones[2] or alkanamides[3,4] (**2**) result in chlorination-iminomethylation with substitution of the carbonyl O-atom by chlorine to give products of the type **3**.



This report describes the reactions of formamide chlorides (**1**) with substituted thioacetamides (**4**). The thioamides used in this study were easily synthesized from methyl ketones by the Willgerodt-Kindler reaction.

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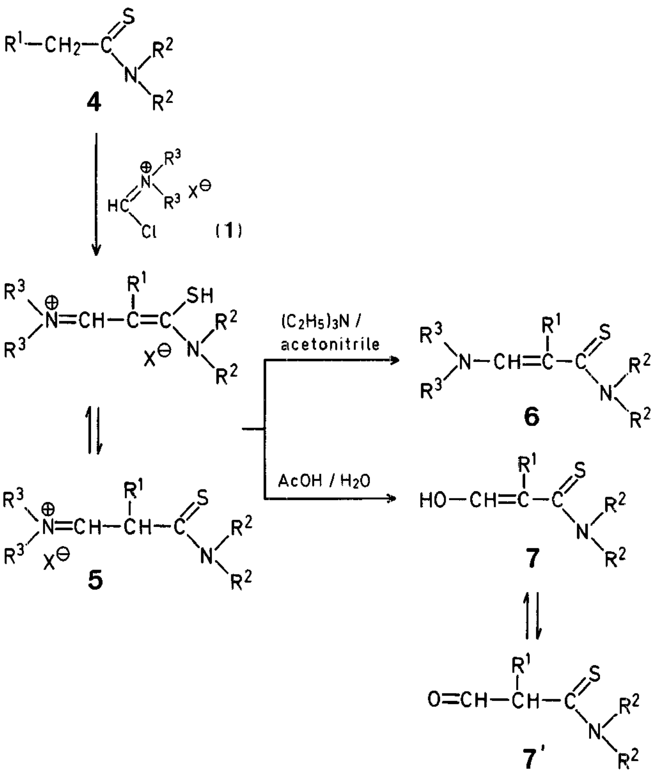
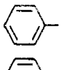
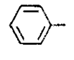
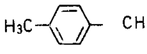
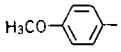
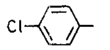
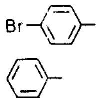
The reaction of equimolar quantities of the reactants **1** with alkanethioamides **4** resulted in the formation of iminomethylation products **5**. These 3-mercapto-2-propeniminium salts are obtained in yields of >50%.



Surprisingly, substitution of the thioxo group by chlorine was not observed. The use of an increased quantity of reagent **1** did not show any effect on the yields of **5**. The 3-mercapto-2-propeniminium salts **5** having a morpholine amide group are best isolated as colourless crystalline perchlorates ($X = ClO_4$). These compounds decompose upon prolonged exposure to air, probably by hydrolysis. In closed vessels and at low temperatures, they can be stored unchanged for several weeks. Thioamides **4** having amide amino groups other than morpholino, for example, piperidino, pyrrolidino, or *N*-methylanilino, did not give crystalline iminium salts **5**. The same is true for propanethiomorpholide [**4**, $R^1 = CH_3$, $N(R^2)_2$ = morpholino]. In these cases, pasty materials were obtained which show similar chemical behaviour as the crystalline products **5** having an amide morpholino group.

The analytical and spectrometric data of the 3-mercapto-2-propeniminium salts **5** as well as their chemical behaviour confirm the proposed structures. The iminium salts **5** are deprotonated by bases to give the corresponding 3-aminopropenethioamides **6**. Hydrolysis of the iminium salts **5** results in the formation of 3-hydroxypropenethioamides (**7**) which may be in equilibrium with the 3-oxopropanethioamides **7'** (see **7 g**).

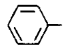
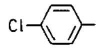
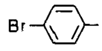
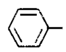
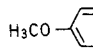
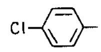
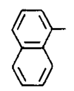
Table 1. 3-Mercapto-2-propeniminium Perchlorates (**5**, $X = ClO_4$, $R^2—R^2 = CH_2—CH_2—O—CH_2—CH_2$)

5	R^1	R^3	R^3	Yield [%]	m.p. (dec.) [°C]	Molecular formula[a]
a[b]		CH_3	CH_3	76	140–141°	$C_{15}H_{21}N_2OS/ClO_4$ (376.9)
b		—(CH₂)₄—		81	118–119°	$C_{17}H_{23}N_2OS/ClO_4$ (402.9)
c	H₃C	CH_3	CH_3	51	138–139°	$C_{16}H_{23}N_2OS/ClO_4$ (390.9)
d	H₃CO	CH_3	CH_3	69	156–157°	$C_{16}H_{23}N_2O_2S/ClO_4$ (406.9)
e	Cl	CH_3	CH_3	73	173°	$C_{15}H_{20}ClN_2OS/ClO_4$ (411.3)
f	Br	CH_3	CH_3	49	151–153°	$C_{15}H_{20}BrN_2OS/ClO_4$ (455.8)
g		—(CH₂)₄—		60	153–155°	$C_{21}H_{25}N_2OS/ClO_4$ (453.0)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.39; H, ±0.25; Cl, ±0.21; N, ±0.34; S, ±0.40. Exceptions: **5a**; N, +0.42; **5b**; N, −0.49.

[b] ^{1}H-N.M.R. (CF_3COOH/TMS_{int}): $\delta = 7.85$ (d, 1H, $J = 7$ Hz); 7.40 (s, 5H); 5.58 (d, 1H, $J = 7$ Hz); 3.85 (m, 8H); 3.60 ppm (s, 6H).

Table 2. 2-Substituted 3-Dialkylaminopropenethioamides (**6**, amide amino group = morpholino) and 3-Hydroxypropenethioamides (**7**, amide amino group = morpholino)

Product	R^1	R^2	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	I.R. (KBr) ν [cm⁻¹]	U.V. (acetonitrile) λ_{max} [nm] (log ε)
6a[b]		CH_3	CH_3	79	107–108° (methanol)	$C_{15}H_{20}N_2OS$ (276.4)		298 (3.94), 409 (2.88)
6e	Cl	CH_3	CH_3	99	97° (cyclohexane)	$C_{15}H_{19}ClN_2OS$ (310.8)		253 (3.82), 302 (4.21), 318 sh (4.20), 411 (3.17)
6f[c]	Br	CH_3	CH_3	91	99° (cyclohexane)	$C_{15}H_{19}BrN_2OS$ (355.3)		256 (4.11), 315 sh (4.49), 322 (4.50), 409 (3.41)
7a[d]		–		81	129–130° (*n*-propanol)	$C_{13}H_{15}NO_2S$ (249.3)	3110 (OH)	246 (4.02), 282 (4.19), 369 (2.98)
7d	H₃CO	–		96	110–111° (methanol)	$C_{14}H_{17}NO_3S$ (279.4)	3100 (OH)	252 sh (4.43), 276 (4.52)
7e	Cl	–		95	131° (methanol)	$C_{13}H_{14}ClNO_2S$ (283.8)	3110 (OH)	254 sh (4.12), 281 (4.22)
7g[e]		–		90	131° (cyclohexane)	$C_{17}H_{17}NO_2S$ (299.4)	1709 (C=O)	277 (4.43), 284 (4.52)

[a] See Table 1.

[b] M.S.: *m/e* = 276 (M^+, 4%), 243 (28), 232 (100), 158 (60), 149 (36), 115 (80), 109 (60).

[c] ^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 7.27$ (d, 2H, $J = 8$ Hz); 6.93 (d, 2H, $J = 8$ Hz); 6.17 (s, 1H); 3.6 (m, 8H); 2.93 ppm (s, 6H).

[d] From **5a**.

[e] This product exists mainly as **7'g** in the solid state.

The reaction of formamide chlorides (**1**) with substituted thioacetamides (**4**) described here[5] provides a new, convenient route to 2-substituted 3-amino- (**6**) and 3-hydroxypropenethioamides (**7**). Related compounds possessing different substitution patterns have hitherto been synthesized by addition of enamines to isothiocyanates[6-12], reaction of amines with 3-aminodithioacrylic esters[13], addition of hydrogen sulfide to 3-aminoacrylonitriles[12,14], reaction of (substituted) thioacetamides with dimethylformamide dimethyl acetal[15], ring cleavage of trithiones with amines[16], or addition of thioacetic acid to 3-aminopropynal[17].

3-Mercapto-2-propeniminium Salts (5); General Procedure:
Phosphoryl chloride (1.54 g, 0.01 mol) is added dropwise to a stirred, cooled solution of an *N,N*-disubstituted formamide (0.01 mol) in tetrachloromethane (5 ml). Then, the substituted thioacetamide **4** (0.01 mol) is added and the mixture is heated to gentle boiling for 30 min. To the resultant solution, glacial acetic acid (8 ml) and 70% perchloric acid (1.5 ml) are added. Product **5** ($X = ClO_4$) is precipitated by the addition of ether, isolated by suction, and recrystallized from glacial acetic acid.

3-Dialkylaminopropenethioamides (6); General Procedure:
Triethylamine (1.2 g, 0.012 mol) is added to the solution of the appropriate 3-mercapto-2-propeniminium perchlorate **5** ($X = ClO_4$; 0.01 mol) in acetonitrile (10 ml). The mixture is then diluted with water and the precipitated product **6** is isolated by suction and recrystallized.

3-Hydroxypropenethioamides (7); General Procedure:
A mixture of the appropriate 3-mercapto-2-propeniminium perchlorate **5** ($X = ClO_4$; 0.01 mol), glacial acetic acid (7 ml), and water (7 ml) is heated to boiling for ~ 1 min, and the solution then diluted with water (50 ml). After the resultant oily product has solidified it is isolated by suction, dried, and recrystallized.

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