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A reaction of thioamides with zinc ammoniates leading to simple amidines. Discovery of a new zwitterionic monomethylamidine

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The reacion of thioamides with the R_1R_2N–ZnCl ammoniates leads to *N*-mono-, *N*,*N*′-di-, *N*,*N*-disubstituted, and unsubstituted amidines with high concentrations of amines in absolute ethanol. The efficient direct formation of the *N*,*N*′-dimethylamidine can be explained by a greater reactivity of methylamine compared with dimethylamine. Discovery of a new zwitterion (induced by a carbonyl oxygen) suggests that the stabilization in the thymine *N*-methylamidine is too slight to prevent the subsequent reaction with methylamine.

KEY WORDS: simple amidines; primary and secondary thioamides; zinc ammoniates.

The biological and non-biological importance of amidines is well-known and has made them widely studied molecules [1]. The most common procedures for the preparation of amidines are the reactions of nitriles, amides, thioamides, and their derivatives with amines [2]. Many variations of a classical Pinner synthesis, the Forsell reaction, fusion with ammonium salts, imidoyl halides, and Vilsmeier reagents are still widely used. The reaction of thioamides with amines or concentrated ammonium hydroxide proceeds in the presence of mercury(II) chloride, iodine, or sodium methoxide [3]. *N*,*N*′-Disubstituted amidines formed upon treatment of the mono-substituted derivative with molten amine salts [4]. 1-Amidinoalkylthymines were obtained from the appropriate nitriles in the presence of 20–22% aqueous ammonium sulfide solution and pyridine [5].

According to literature data on zinc ammoniates, addition of an amine or ammonia to one mole of the zinc salt could result in the formation of 1:1 complexes [6]. These ammines demonstrated a tendency to ammonolysis. For example, NH_2ZnCl and NH_4Cl were formed by the action of gaseous NH_3 on $ZnCl_2$ [7]. In the presence of RNHHgCl, the Forster reaction of RNHCSNHR proceeds efficiently to provide $RN=C(NHR)_2$ [3a]. Consequently, new syntheses of simple amidines, starting from primary or secondary thioamides and zinc ammoniates, are discussed in this paper.

The reaction of primary thioamide **1** with 33% methylamine or 33% dimethylamine in absolute ethanol and anhydrous zinc chloride provides an easy access to methyl-substituted simple amidines. The reaction of primary thioamides with amines, producing secondary thioamides, requires a much longer reaction time when conducted in the absence of $ZnCl_2$ [5]. The close similarity of the ^1H and ^{13}C spectra in DMSO-d_6 of **1a** in the presence and absence of $ZnCl_2$ can be taken as evidence supporting the assumption that this thioamide does not react with zinc chloride. The new reaction takes place at ambient temperature, according to Scheme 1. The best results were obtained when one mole of $ZnCl_2$ and an excess of the concentrated methylamine or dimethylamine solution were employed.

The lower yield of *N*,*N*-dimethylamidine **2** (78%), compared with **3a** (97%), is explained by the fact that the thione–thiol tautomerism in solution is necessary for carrying out the reaction. *N*,*N*′-Dimethylamidine **3a** can be obtained because the *N*-methylthiocarbamoyl intermediate, bearing the mobile CSNH hydrogen atom, gives rapid and a facile tautomeric transformation of the thione form to the corresponding thiol form. In an *N*,*N*-disubstituted thioamide the amino functionality is fixed by substitution and no tautomerism is possible; the product is highly hindered to substitution pathways. It exists in thione form rather than in thiol form. The procedure outlined here is also applicable to the synthesis of **3b** from thioamide **1b** (very susceptible to the reversal of the Michael addition reaction) and seems to have general applicability.

Thioamides are rarely used for acylation of amines owing to the difficulties in their purchase contrary to other reagents, e.g. acyl halides or acid anhydrides. The reduced reactivity of thioamides can be overcome by activation of an amine by conversion to the appropriate ammoniate reagent. As in the case of 40% methylamine in water, acylation can be achieved by thioamide **1a** and a good 92% yield of secondary amide **4** is obtained

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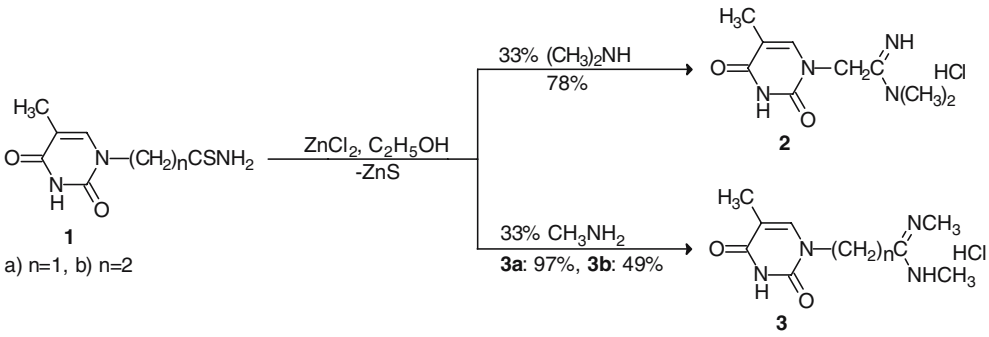


Scheme 1. Syntheses of *N*,*N*-dimethyl- and *N*,*N*′-dimethylamidines.

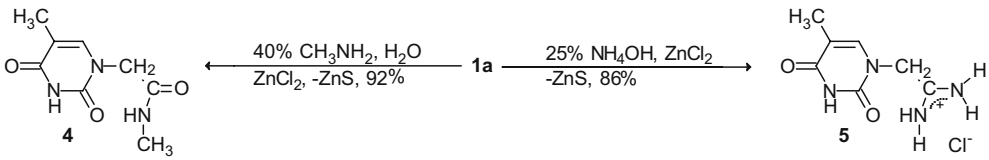
(Scheme 2). Mechanistically, this acylation reaction might proceed via a hydrolysis of the secondary thioamide intermediate and elimination of zinc sulfide. Indeed, when the reagents were diluted with water the reaction took a different course leading to a mixture of products including *N*-methyl(1-thyminyl)thioacetamide. This can be regarded as evidence for the secondary thioamide intermediate. The effect of $ZnCl_2$ on the reaction of **1a** with 25% ammonium hydroxide was investigated. In contrast to aqueous methylamine, the latter was able to give unsubstituted simple amidine **5**.

Some representative derivatives **7--8** that have been prepared starting from α-(1-thyminyl)-*m*-thiotoluamide (**6**), are an extension of the reaction for aryl thioamides (Scheme 3). A weakening reactivity was observed for **6** upon treatment with the $ZnCl_2$–methylamine reagent; monomethylamidine **7** was obtained in 62% yield.

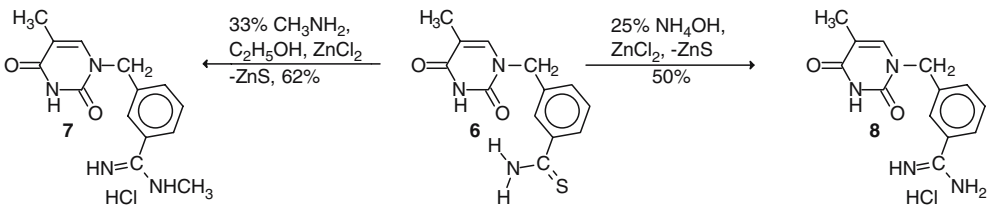
An interesting deviation from the typical behavior was observed for the reaction in which **6** was decomposed into α-(1-thyminyl)-*m*-tolunitrile (**9**) by loss of H_2S in the presence of zinc chloride and dialkylamines (Scheme 4). This can be explained by a steric hindrance of the dimethyl or diethyl group in the intermediate. The substitution in the amidinium residue yields a system less stable than that in **8**. There are literature reports on a similar decomposition to have occurred upon addition of mercuric chloride [8], amines [9] or ammonium salts [10]. Also, 4-amino(thiobenzamide) (**10**) subjected to the above reaction conditions afforded nitrile **11**.

Another example, when reaction of thio-*p*-toluamide (**12**) with the $ZnCl_2$–methylamine reagent was carried out, is furnished by the formation of *N*-methylamidine **13** (45%). For some reactions the side products were isolated and identified. The reaction of thio-4-fluorobenzamide (**14**) affords *N*,*N*′-dimethylamidine **15** (54%) and by-product **16** was separated by chromatography (Scheme 5). This fact means that it is possible that the first step in the general mechanism is due to a transamination reaction of the primary thioamide. The reaction proved to be less satisfactory with respect to weaker stabilization of the products.

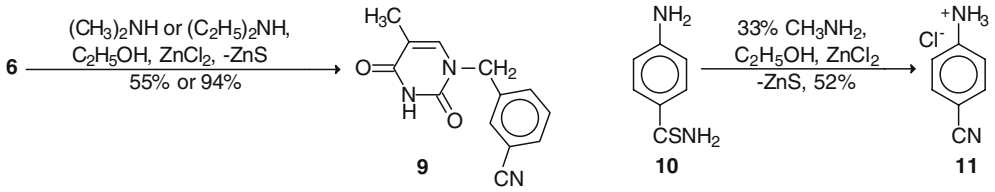
Secondary thioamide **17** reacts to produce a mixture of *N*-methylamidine **18** and zwitterion **19**, opening up a convenient way to monomethylamidines in the case of high reactivity of primary thioamides (Scheme 6). This thioamide is transformed to the mixture of products with the ammonia–$ZnCl_2$ reagent, although in very low yield, while thioamide **1a** gives *N*,*N*′-dimethylamidine **3a**



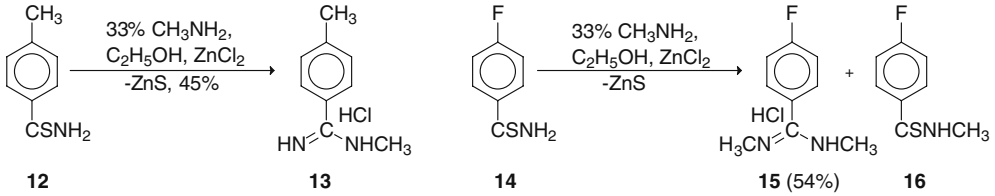
Scheme 2. Syntheses under aqueous conditions.



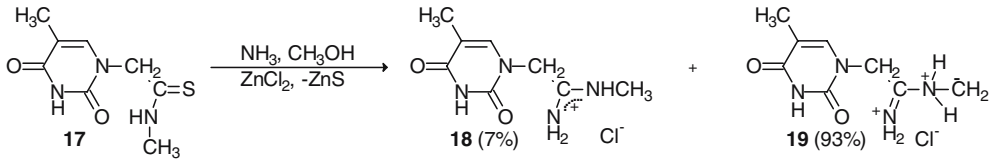
Scheme 3. Syntheses of amidines from thiobenzamides.



Scheme 4. The use of the dialkylamine–$ZnCl_2$ reagents leads to a less satisfactory preparative result; the product is nitrile.



Scheme 5. The electron-withdrawing fluorine substituent in the phenyl group increases the reactivity, while the methyl group slows it down.



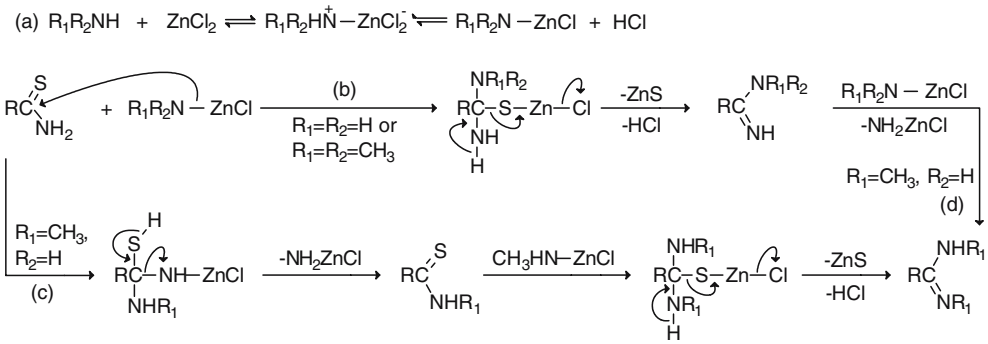
Scheme 6. Synthesis of *N*-methylamidines from a secondary thioamide.

directly when reacted with methylamine. Thus, **17** can be regarded as the intermediate in the latter reaction. On the basis of spectroscopic evidence as well as by comparison with earlier works discussing similar problems [11,12] the proof has been furnished that the thymine monomethylamidine mainly exists in the zwitterionic form. The proton spectrum shows a predominance of **19** and a small quantity of nonzwitterionic product **18** (less stability). Two separate N*H* signals (one of them $^{+}NH_2$ and the other $^{+}NH_2CH_2^{-}$) and only one NCH_2^{-} singlet corresponding to structure **19** are present owing to severe electrostatic repulsion. The position of these signals and their integration curves demonstrate the existence of an intramolecular interaction. The formation of **19** very probably involves at first an ionization in the methyl group leading to the anion and the proton is then migrated at the amino nitrogen.

Nucleophilic attack at the thiocarbamoyl group leading to the amidine could be facilitated by the presence of the R_1R_2NZnCl ammoniates, produced by ammonolysis of the appropriate ammines ($ZnCl_2$·NH R_1R_2). A multi-step mechanism for their formation has been proposed (Scheme 7). The reaction of an amine with $ZnCl_2$ (a) and the nucleophilic attack on the carbon of a primary thioamide by the nitrogen of the reagent (substitution of the mercapto group) (b) take place. Experimental details given in this publication provide support for this belief. The catalytic influence of $ZnCl_2$ on the transamination reaction has been recognized (c). The addition of $ZnCl_2$ to the reaction mixture accelerated the transformation of primary thioamides to secondary thioamides and simple amidines. It may be assumed, however, that the *N*-substituted simple amidine can be converted into the *N*,*N*′-disubstituted derivative (d).

1. Experimental

Melting points are uncorrected and were determined by using Boetius melting-point apparatus. NMR spectra were recorded on a Varian 300 Gemini spectrometer in DMSO-d_6 solutions with TMS as a standard (unless otherwise indicated), and IR spectra on a Bruker 113v FT-IR spectrometer (KBr). High resolution mass spectra were obtained using an AMD 402 or 604 mass spectrometer in the EI or FAB mode, respectively. Thin-layer chromatography (TLC) was performed with Merck silica gel $60F_{254}$ plates (0.25 mm thickness) in the following developing solvent systems: 44:8:1, 11:4:1, 7:5:2 $CHCl_3$–CH_3OH–25%NH_4OH. All final samples were dried first in an oven at 110 °C and then stored in a vacuum desiccator over P_2O_5. 33% Methylamine in absolute ethanol, 40% methylamine in water, diethylamine and anhydrous zinc chloride were available from Aldrich. 33% Dimethylamine in absolute ethanol was purchased from Fluka. (1-Thyminyl)thioacetamide (**1a**) [13], 3-(1-thyminyl)thiopropionamide (**1b**) [5], α-(1-thyminyl)(thio-*m*-toluamide) (**6**) [5],



Scheme 7. A probable general mechanism.

4-amino(thiobenzamide) (**10**) [14], 4-methyl(thiobenzamide) (**12**) [5,15], 4-fluoro(thiobenzamide) (**14**) [16], and *N*-methyl(1-thyminyl)thioacetamide (**17**) [5] were obtained according to the literature.

*1.1. Reaction of thioamide **1** with anhydrous methylamine or dimethylamine*

Primary thioamide **1** (0.9962 g, 0.005 mol) was added to a mixture of anhydrous zinc chloride (0.8177 g, 0.006 mol) and 33% methylamine or 33% dimethylamine solution in absolute ethanol (20 cm^3). A precipitate was formed immediately and some heat was evolved. The reaction mixture was then stirred for 1 h at room temperature in a stoppered flask. After evaporation of the solvent, the white residue was mixed with 1 N hydrochloric acid (30 cm^3) and warmed until the solid had dissolved. The mixture was filtered to remove a small amount of the precipitate, and the filtrate evaporated under diminished pressure. Purification of the crude product was performed by crystallization from methanol–water. After cooling, the respective hydrochloride salt **2** or **3** was separated out as white crystals.

N,*N*-Dimethyl(1-thyminyl)acetamidine hydrochloride (**2**): 78%; mp > 310 °C; ν_{max} 3157, 3016, 2988, 2950, 2898, 2836, 1685, 1650, 1626, 1507, 1481, 1429, 1386, 1353, 1273, 1154, 1083, 1061, 1049, 1022 cm^{-1}; δ_H 1.77 (d, 3H, J = 1.1 Hz, CH_3), 3.15 (s, 6H, NCH_3), 4.84 (s, 2H, CH_2), 7.43 (d, 1H, J = 1.1 Hz, C6H), 8.79 (br s, 2H, NH_2), 11.48 (s, 1H, N3H); δ_H (D_2O, DSS) 1.92 (d, 3H, J = 1.4 Hz, CH_3), 3.21 (s, 3H, NCH_3), 3.30 (s, 3H, NCH_3), 4.96 (s, 2H, CH_2), 7.45 (d, 1H, J = 1.4 Hz, CH_2); δ_C (D_2O, DSS) 14.2, 42.2, 42.5, 50.4, 115.3, 144.3, 155.0, 164.6, 169.4; LRMS (EI): 210(55), 165(11), 140(21), 96(16), 71(100); HRMS (EI): $M^{+\cdot}$, found 210.1115. $C_9H_{14}N_4O_2$ requires 210.1117.

(*EZ*)-*N*,*N*′-Dimethyl(1-thyminyl)acetamidine hydrochloride (**3a**): 97%; mp 310–311 °C; ν_{max} 3291, 3237, 3133, 3049, 3007, 2986, 2949, 2799, 2777, 1718, 1690, 1675, 1576, 1465, 1419, 1388, 1361, 1343, 1264, 1198 cm^{-1}; δ_H 1.77 (d, 3H, J = 0.8 Hz, CH_3), 2.82 (s, 3H, NCH_3), 3.00 (s, 3H, NCH_3), 4.89 (s, 2H, CH_2), 7.50 (d, 1H, J = 1.4 Hz, C6H), 9.09 (s, 1H, NH), 9.17 (s, 1H, NH), 11.52 (s, 1H, N3H); δ_C 12.1, 29.1, 29.2, 45.8, 110.3, 140.5, 151.2, 162.2, 164.5; LRMS (EI): 210(19), 139(4), 96(4), 84(11), 71(100); HRMS (EI): $M^{+\cdot}$, found 210.1121. $C_9H_{14}N_4O_2$ requires 210.1117.

(*EZ*)-*N*,*N*′-Dimethyl(1-thyminyl)propionamidine hyd rochloride (**3b**): It was obtained with cautious evaporation. 49%; mp 224–225 °C; ν_{max} 3292, 3154, 3045, 3019, 2830, 2747, 1707, 1663, 1589, 1480, 1426, 1389, 1363, 1356, 1313, 1251, 1227, 1211, 1191, 1150 cm^{-1}; δ_H 1.76 (s, 3H, CH_3), 2.77 (s, 3H, NCH_3), 2.87 (t, 2H, J = 6.4 Hz, CH_2), 3.01 (s, 3H, NCH_3), 3.94 (t, 2H, J = 6.6 Hz, N1CH_2), 7.57 (d, 1H, J = 0.9 Hz, C6H), 9.35 (br s, 2H, NH), 11.27 (br s, 1H, N3H) ; δ_C 12.0, 28.8, 29.5, 29.9, 43.6, 108.9, 141.1, 151.0, 164.3; δ_C (D_2O, TMS) 14.1, 30.9, 32.3, 32.5, 47.4, 114.1, 144.8, 154.7, 167.1, 169.5; HRMS (FAB, NBA): MH^+, found 225.1332. $C_{10}H_{17}N_4O_2$ requires 225.1352. The EI spectrum could not be obtained because decomposition to thymine took place: m/z 126(100).

*1.2. Reaction of thioacetamide **1a** with aqueous methylamine or ammonium hydroxide*

A mixture of **1a** (0.9962 g, 0.005 mol), $ZnCl_2$ (0.8177 g, 0.006 mol), and 40% methylamine in water (20 cm^3) was left to react as described for **2**. Product **4** was purified by crystallization from methanol–water.

N-Methyl(1-thyminyl)acetamide (**4**): 92%; mp 291–292 °C; ν_{max} 3523, 3331, 3152, 3088, 2995, 2957, 2903, 2834, 1676, 1561, 1484, 1429, 1389, 1379, 1360, 1267, 1236, 1169, 1155, 1017 cm^{-1}; δ_H 1.75 (d, 3H, J = 1.1 Hz, CH_3), 2.61 (d, 3H, J = 4.7 Hz, NCH_3), 4.25 (s, 2H, N1CH_2), 7.43 (d, 1H, J = 1.1 Hz, C6H), 8.03 (br q, 1H, J = 4.4 Hz, CONH), 11.25 (br s, 1H, N3H); δ_C 11.8, 25.5, 49.7, 108.0, 142.3, 151.0, 164.5, 167.4; LRMS (EI): 197(24), 140(100), 111(3), 96(65), 69(43); HRMS (EI): $M^{+\cdot}$, found 197.0805. $C_8H_{11}N_3O_3$ requires 197.0801.

A mixture of $ZnCl_2$ (0.8177 g, 0.006 mol) and 40% methylamine solution in water (5 cm^3) was diluted with water (15 cm^3). After cooling, **1a** (0.9962 g, 0.005 mol) was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed under

vacuum and the solid was treated with 1 N HCl (30 cm^3). After evaporation of the solvent, the residue was crystallized from methanol (50 cm^3) to give **17** (0.1617 g).

(1-Thyminyl)acetamidine hydrochloride (**5**): A mixture of **1a** (0.9962 g, 0.005 mol), $ZnCl_2$ (0.8177 g, 0.006 mol), and 25% ammonium hydroxide (20 cm^3) was stirred for 24 h at room temperature. Purification was performed as described above. Crystalline product **5** was separated after cooling of a methanolic solution (50 cm^3). 86%; mp 299–302 °C (dec.); ν_{max} 3304, 3226, 2982, 2928, 2799, 2760, 1707, 1674, 1471, 1456, 1406, 1363, 1348, 1256, 1231, 1149, 1110, 1069, 1052, 1016 cm^{-1}; δ_H 1.76 (d, 3H, J = 1.1 Hz, CH_3), 4.69 (s, 2H, CH_2), 7.58 (d, 1H, J = 1.4 Hz, C6H), 9.19 (s, 2H, NH), 9.21 (s, 2H, NH), 11.43 (s, 1H, N3H); δ_C 12.0, 47.3, 109.6, 141.1, 151.2, 164.6, 166.5; LRMS (EI): 182(39), 165(5), 140(100), 111(5), 96(19); HRMS (EI): $M^{+\cdot}$, found 182.0793. $C_7H_{10}N_4O_2$ requires 182.0804.

1.3. Reaction of thiobenzamide **6** with anhydrous amines or ammonium hydroxide

A mixture of **6** (0.5000 g, 0.0018 mol), $ZnCl_2$ (0.2970 g, 0.0022 mol), and 33% methylamine in ethanol (10 cm^3) was stirred overnight at room temperature. Working-up as in the preceding section provided product **7** after crystallization from methanol–isopropanol and recrystallization from methanol.

(*Z*)-*N*-Methyl-α-(1-Thyminyl)-*m*-toluamidine hydrochloride (**7**): 62%; mp 191–192 °C; ν_{max} 3339, 3298, 3199, 3162, 3039, 2951, 2925, 2834, 1708, 1673, 1626, 1587, 1544, 1464, 1442, 1421, 1382, 1350, 1249, 1228 cm^{-1}; δ_H 1.77 (d, 3H, J = 1.1 Hz, CH_3), 3.01 (d, 3H, J = 4.3 Hz, NCH_3), 4.93 (s, 2H, CH_2), 7.57–7.80 (m, 5H, C_6H_4, C6H), 9.04 (s, 1H, NH), 9.57 (s, 1H, NH), 9.95 (br q, 1H, J = 4.0 Hz, NH), 11.38 (s, 1H, N3H); δ_C 12.0, 29.6, 49.7, 109.2, 127.3, 127.4, 129.2, 129.4, 132.4, 138.0, 141.3, 151.1, 163.4, 164.4; LRMS (EI): 272(37), 259(7), 241(23), 148(44), 116(100); HRMS (EI): $M^{+\cdot}$, found 272.1256. $C_{14}H_{16}N_4O_2$ requires 272.1273.

(*Z*)-α-(1-Thyminyl)-*m*-toluamidine hydrochloride (**8**): A mixture of thioamide **6** (0.2753 g, 0.001 mol), $ZnCl_2$ (0.2000 g, 0.0015 mol), and 25% NH_4OH (10 cm^3) was stirred for 2 days at room temperature and evaporated to dryness. The product was obtained by treating with 1 N HCl, evaporation, and crystallization of the residue from isopropanol–methanol–monoglyme. Product **8** was recrystallized from methanol. 50%; mp > 300 °C (it starts to decompose at 174 °C); ν_{max} 3327, 3156, 3056, 2822, 1675, 1521, 1473, 1436, 1383, 1353, 1292, 1243, 1216, 1130, 1100, 1015, 966, 911, 807, 783 cm^{-1}; δ_H 1.77 (s, 3H, CH_3), 4.92 (s, 1H, CH_2), 7.57–7.83 (m, 5H, C_6H_4, C6H), 9.29 (br s, 4H, H_2NCNH_2), 11.39 (br s, 1H, N3H); δ_C 12.0, 49.6, 109.0, 127.0, 127.2, 128.4, 129.2, 132.6, 137.8, 141.0, 150.8, 164.0, 165.3; HRMS (FAB, NBA): MH^+, found 258.1118. $C_{13}H_{14}N_4O_2$ requires 258.1117.

1.4. Conversion of thioamide **6** or **10** to a nitrile

A mixture of **6** (0.5000 g, 0.0018 mol), zinc chloride (0.2970 g, 0.0022 mol), and 33% dimethylamine in ethanol (10 cm^3) failed to yield a simple amidine by the same procedure as that used for preparing **2**. This mixture was transformed into nitrile **9** (ν_{max} 3162, 3102, 2226 cm^{-1}) in 55% yield. Repeating the same experiment using 1:1 mixture of diethylamine and methanol led to **9** in 94% yield. In both cases the product was found to be identical with the authentic sample. Similarly, a mixture of thioamide **10** (0.7611 g, 0.005 mol), zinc chloride (0.8177 g, 0.006 mol), and 33% methylamine in ethanol (10 cm^3) was reacted to afford nitrile **11** (ν_{max} 2574, 2536, 2236 cm^{-1}) as the hydrochloride salt in 52% yield, under the reaction conditions employed above.

1.5. Reaction of thiobenzamide **12** or **14** with methylamine

After overnight stirring at room temperature, the reaction mixture of **12** (0.7561 g, 0.005 mol) or **14** (0.7760 g, 0.005 mol) and 33% methylamine in ethanol (10 cm^3) in the presence of $ZnCl_2$ (0.8177 g. 0.006 mol) was worked-up analogously to other amidines and afforded **13** or **15**, respectively.

(*Z*)-*N*-Methyl-*p*-toluamidine hydrochloride (**13**): 45%; mp 213–214 °C; ν_{max} 3342, 3302, 3215, 3061, 2994, 2925, 2889, 2791, 1670, 1624, 1612, 1576, 1511, 1457, 1420, 1380, 1297, 1190, 1171, 1131 cm^{-1}; δ_H 2.40 (s, 3H, CH_3), 3.01 (s, 3H, NCH_3), 7.40 (d, 2H, J = 8.0 Hz), 7.75 (d, 2H, J = 8.2 Hz), 9.10 (br s, 1H, NH), 9.56 (br s, 1H, NH), 9.96 (br s, 1H, NH); δ_C 21.0, 29.6, 125.7, 128.0, 129.4, 143.7, 163.0; LRMS (EI): 148(23), 147(100), 132(17), 118(80), 105(4); HRMS (EI): $M^{+\cdot}$, found 148.1004. $C_9H_{12}N_2$ requires 148.1001.

(*EZ*)-*N*,*N*′-Dimethyl-4-fluorobenzamidine hydrochloride (**15**): 54%; mp 244–245 °C; ν_{max} 3174, 3106, 3049, 3033, 3000, 2927, 2877, 2761, 1653, 1610, 1593, 1583, 1513, 1457, 1442, 1428, 1389, 1369, 1231, 1221 cm^{-1}; δ_H 2.83 (br s, 3H, NCH_3), 3.02 (br s, 3H, NCH_3), 7.47 (t, 2H, J = 8.9 Hz), 7.73 (dd, 2H, J = 9.0, 5.3 Hz), 9.80 (br s, 2H, NH); δ_C 29.9, 31.5, 116.2 (d, J = 22.3 Hz), 124.7, 131.2 (d, J = 9.3 Hz), 163.3, 163.9 (d, J = 249.5 Hz); LRMS (EI): 166(19), 165(88), 136(100), 122(45), 109(15); HRMS (EI): $M^{+\cdot}$, found 166.0891. $C_9H_{11}FN_2$ requires 166.0906.

N-Methyl-4-fluoro(thiobenzamide) (**16**): Secondary thioamide **16** was obtained by preparative TLC (commercial $CHCl_3$) and subsequent recrystallization from acetone. 29 mg; mp 89–90 °C; ν_{max} 3322, 3071, 3044, 3011, 2957, 2927, 1734, 1652, 1606, 1594, 1537, 1505, 1438, 1407, 1350, 1247, 1164, 1044, 943, 838 cm^{-1}; δ_H ($CDCl_3$) 3.32 (d, 3H, J = 4.9 Hz, NCH_3), 7.04 (t, 2H,

J = 8.5 Hz), 7.74 (dd, 2H, J = 8.8, 5.2 Hz), 7.81 (br s, 1H, N*H*); δ_C 33.7, 115.4 (d, J = 21.8 Hz), 128.8 (d, J = 9.2 Hz), 137.8 (d, J = 3.4 Hz), 164.4 (d, J = 252.5 Hz), 198.6; LRMS (EI): 169(100), 168(65), 139(95), 136(22), 122(10); HRMS (EI): $M^{+\cdot}$, found 169.0347. C_8H_8FNS requires 169.0362.

1.6. Synthesis of N-methylamidines starting from secondary thioamides

To a solution of zinc chloride (0.0500 g, 0.0004 mol) in a saturated methanolic solution of ammonia (10 cm^3), secondary thioamide **17** (0.0500 g, 0.0002 mol) was added and the suspension was stirred magnetically overnight at room temperature. The substrate **17** was sluggish in reacting with ammonia. The next day, the reaction mixture was evaporated to dryness in vacuo. The siropous residue was evaporated with two 50 cm^3-portions of 1 N HCl and crystallized from water to recover the unaltered starting material (0.0350 g). The filtrate and washings were combined and evaporated. The resulting crude product was recrystallized twice from isopropanol to afford white crystals (9 mg, mp 265–267 °C). TLC (11:4:1 and 7:5:2 $CHCl_3$–CH_3OH–NH_4OH) showed two UV spots corresponding to two isomers. The mixture contained both N-methylamidine **18** and zwitterion **19** of the lower R_f value which were not separated.

(*Z*)-*N*-Methyl(1-thyminyl)acetamidine hydrochloride (**18**): 7% (by NMR), ν_{max} 3504, 3343, 3063, 2821, 1690, 1472, 1414, 1385, 1359, 1317, 1255, 1236, 1150, 1045, 1020, 960, 899, 776, 546, 482 cm^{-1}; δ_H 1.76 (s, 3H, CH_3), 2.84 (d, 3H, J = 5.0 Hz, NCH_3), 4.65 (s, 2H, CH_2), 7.49 (s, 1H, C6*H*), 8.91 (s, 1H, N*H*), 9.23 (s, 1H, N*H*), 9.51 (s, 1H, N*H*), 11.48 (s, 1H, N3*H*); zwitterion **19**: 93% (by NMR); δ_H 1.76 (s, 3H, CH_3), 3.36 (s, 2H, NCH_2^-), 4.62 (s, 2H, CH_2), 7.49 (s, 1H, C6*H*), 8.91 (s, 1.5H, N*H*), 9.06 (s, 1.5H, N*H*), 11.46 (s, 1H, N3*H*); δ_C 12.1, 28.9, 47.5, 109.6, 141.1, 151.2, 164.6, 166.2; LRMS (EI): 196(7), 182(18), 165(100), 140(45); HRMS (EI): $M^{+\cdot}$, found 196.0948. $C_8H_{12}N_4O_2$ requires 196.0960.

In summary, this investigation has demonstrated, for the first time, that the reaction of a thioamide with concentrated amine solutions in the presence of zinc chloride at room temperature leads to the formation of simple amidines. The reaction is complex and, depending upon the experimental conditions, can afford a variety of products in good yields. Great advantages are the simplicity of purification and the shortened reaction time. The NMR, IR, and MS data are in excellent agreement with the structures proposed.

References

[1] (a) J.D.A. Tyndall, B. Pfeiffer, G. Abbenante and D.P. Fairlie, Chem. Rev. 105 (2005) 793; (b) R.R. Tidwell and D.W. Boykin, in: *DNA and RNA Binders: from Small Molecules to Drugs*, Vol. 2, (eds.), M. Demeunynck, C. Bailly and W.D. Wilson (Wiley-VCH Verlag, Weinheim, 2003) ch. 16; (c) P.L. Barker, P.L. Gendler and H. Rapoport, J. Org. Chem. 46 (1981), 2455.

[2] (a) P.J. Dunn, in: *Comprehensive Organic Functional Group Transformations*, (eds.), A.R. Katrizky, O. Meth-Cohn and C.W. Rees (Elsevier, Oxford, 1995); (b) G.V. Boyd, in: *The Chemistry of Amidines and Imidates*, Vol. 2, (eds.), S. Patai and Z. Rappoport (Wiley, Interscience, Chichester, 1991) ch. 8.

[3] (a) A. Bernthsen, Ann. 184 (1876) 290 and 321; (b) A. Bernthsen, Ann. 192 (1878) 1; (c) A. Bernthsen, Ber. 9 (1876) 429; (d) G.R. Pettit and L.R. Garson, Can. J. Chem. 43 (1965) 2640; (e) Merck & Co., Inc., Neth. Appl. 6,607,412, Dec. 9, 1966; Chem. Abstr. 67 (1967) 3090y.

[4] H. Leo, Ber. 10 (1877) 2133.

[5] J. Spychala, Tetrahedron 56 (2000) 7981.

[6] (a) Z.K. Zubakhina, Tr. Nauch.-Issled. Inst. Osn. Khim. 19 (1969) 105; Chem. Abstr. 74 (1971) 91838w; (b) D.P.N. Satchell and R.S. Satchell, Trans. Faraday Soc. 61 (1965) 1118.

[7] (a) F. Remy, Rev. Chim. Miner. 5 (1968) 935; Chem. Abstr. 70 (1969) 102606q; (b) P.P. Fedorov and P.I. Fedorov, Zh. Fiz. Khim. 45 (1971) 1869; Chem. Abstr. 75 (1971) 122938f.

[8] S. Ishikawa, Sci. Papers Inst. Phys. Chem. Research (Tokyo) 7 (1928) 301; Chem. Abstr. 22 (1928) 1343; Chem. Z. 99 I (1928) 1765.

[9] M. Raffo and G. Rossi, Gazz. Chim. Ital. 44 I (1914) 104; Chem. Abstr. 9 (1915) 1473.

[10] F. Micheel and Z. Krzeminski, Ann. 575 (1952) 90.

[11] J.D. Halliday, E.A. Symons and P.E. Bindner, Can. J. Chem. 56 (1978) 1470.

[12] T.M. Krygowski and K. Wozniak, in: *The Chemistry of Amidines and Imidates*, Vol. 2, (eds.), S. Patai and Z. Rappoport (Wiley, Interscience, Chichester, 1991) ch. 2.

[13] J. Spychala, Synth. Commun. 27 (1997) 3431.

[14] A.E.S. Fairfull, J.L. Lowe and D.A. Peak, J. Chem. Soc. (1952) 742.

[15] H. Schiff, Chem. Ber. 8 (1875) 439.

[16] (a) L. Stephenson, W.K. Warburton and M.J. Wilson, J. Chem. Soc. C (1969) 861; (b) W. Walter and H.P. Kubersky, J. Mol. Struct. 11 (1972) 207.