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Convenient syntheses of N-methylthioamides: A migration of the H_2S molecule in the thioamide-nitrile system

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Convenient syntheses of N-methylthioamides: A migration of the H_2S molecule in the thioamide-nitrile system

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A number of primary thioamides was prepared from the appropriate aliphatic or aromatic nitriles in high yield and then used in syntheses of secondary thioamides. Two reactions between 4-thiothymine derivatives and methylamine were carried out in order to confirm the rearrangement of the H_2S molecule in 1-(3-cyanopropyl)-4-thiothymine, leading to an N-methylthioamide (via a primary thioamide intermediate) on further reaction with methylamine. 1-[3-(thiocarbamoyl)propyl]-4-thiothymine gave directly the same product. Evidence for the new hydrogen-bond-promoted reaction is provided. The proposed CSNH···O=C2 bonding scheme seems to be plausible.

Keywords: Lawesson's reagent; Primary and secondary thioamides; Rearrangement; 4-Thiouracils

1. Introduction

The thioamides, compounds which have found significant applications as agricultural herbicides, corrosion inhibitors, vulcanization promoters, antioxidants, and have also been recommended as pharmaceutical as well as synthetic and analytical intermediates, can be prepared by a variety of methods. Base or acid-catalyzed addition of hydrogen sulfide to a nitrile group is still used in many modifications [1–7].

During work on secondary (thio)amides, it was found that a commercially available analytical reagent, ammonium sulfide is of value for the synthesis [8]. The reagent has been already applied for the preparation of (1-thyminyl)thioacetamide [9] and 4-hydroxy(thiobenzamide) [10], but the reaction has not been extended to other nitriles. General procedures for the preparation of primary and secondary thioamides in high yields are presented in this article.

2. Results and discussion

The reactions in scheme 1 can be performed in nearly molar proportions with a commercially available aqueous ammonium sulfide solution and pyridine, thus avoiding the use of high

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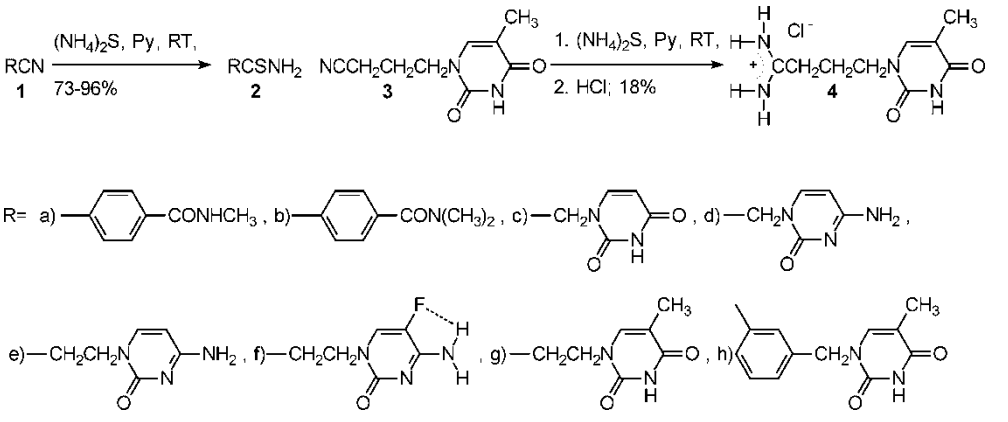


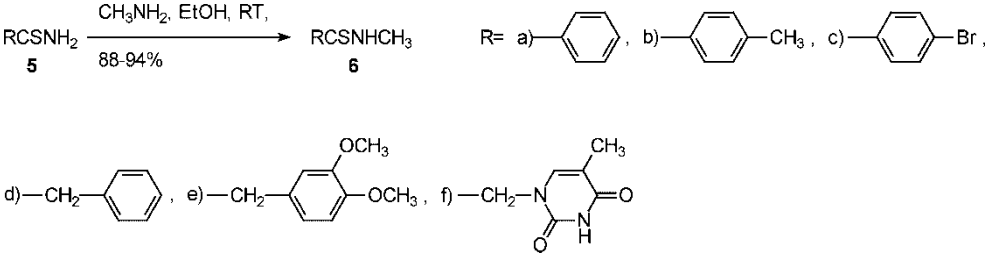
SCHEME 1

concentrations of $(NH_4)_2S$ and anhydrous conditions. It was found that the conversion of nitrile **1** to primary thioamide **2** could be effected simply by shaking the reaction mixture. The reaction was completed at room temperature after two months and the thioamide obtained, usually in good yield (73–96%) and in a state of high purity. A prolonged reaction time leads to the formation of unsubstituted simple amidine **4** from nitrile **3**. This observation suggests that a primary thioamide can play a role of an intermediate in the latter reaction [11].

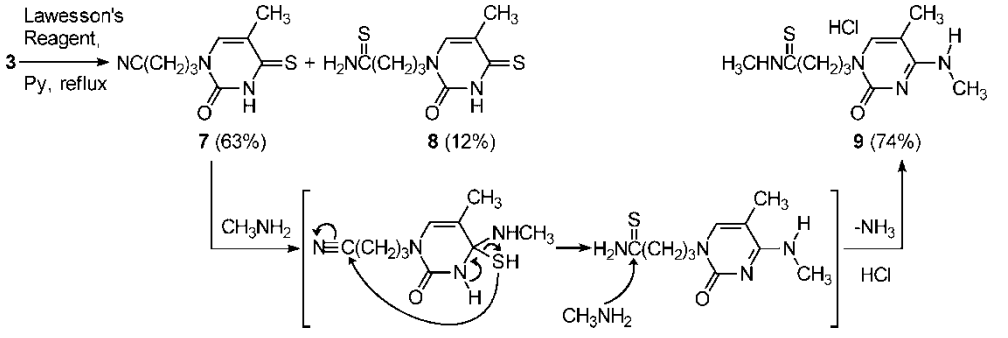
Despite the long reaction time of the aqueous thiation presented in this communication, it seemed to be profitable in view of the convenience in handling and protection of natural environment. The very mild conditions make this reaction useful for the synthesis of thermal sensitive thioamides **2e–g**. The reaction time can be shortened significantly if a large amount of ammonium sulfide is used, but yields are poorer. The reaction leads to an increase in the amount of the corresponding amides. In principle, the progress of the reaction depends on the mole ratio of $(NH_4)_2S$ to a nitrile [1–7].

The preparation of secondary thioamides from primary thioamides has found little attention due to the fact that the latter are usually made from nitriles which can directly yield the former [8, 11–13]. In order to see if the presence of 33% methylamine in absolute ethanol has any effect on primary thioamide **5**, the reaction was carried out for three days at room temperature. It was found possible to prepare secondary thioamide **6** containing either aliphatic or aromatic substituent (scheme 2).

As can be seen from the experimental data, the presented procedure is preparatively useful and affords a new way to a number of secondary thioamides in excellent yields (88–94%), starting from readily available primary thioamides. Great advantages of this method are the simplicity of isolation and purification of the desired products. Attempts to react a primary



SCHEME 2



SCHEME 3

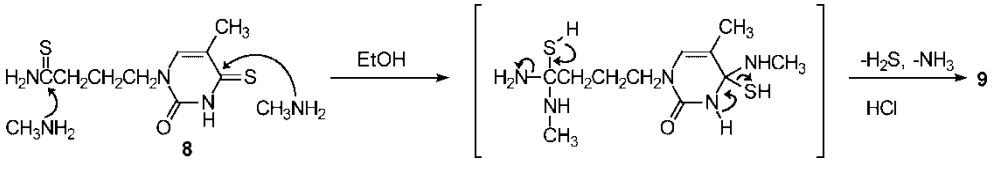
thioamide with dimethylamine, by the same procedure as that used for methylamine, led to a recovery of the starting material.

Thioamides react with primary aliphatic amines by replacement of their amino groups with other amino groups from the reagent as in the preceding section. The transamination reaction does not take place when cyclic thioamides (e.g. 4-thiouracils) are employed as substrates, giving rise to an N^4-substituted cytosine derivative by nucleophilic attack of the amine N atom on the thiocarbamoyl carbon atom. For example, N^4-methyl- or N^4, N^4-dimethyl-2′-deoxycytidine was conveniently obtained starting from 4-thio-2′-deoxycytidine and methylamine or dimethylamine, respectively [14–16].

The reaction between 1-(3-cyanopropyl)-4-thiothymine (**7**) and methylamine proceeds with a rearrangement of the H_2S unit in the thioamide-nitrile system, indicating that the nucleophilic substitution induces the intramolecular thiation of the pendant 3-cyanopropyl group (scheme 3). The migration process of the H_2S molecule takes place such as that the electron lone pair on the sulfur atom is in a position to condense onto the cyano group. The transamination reaction results in the formation of a secondary thioamide (N^4-methylcytosine **9**). The initial product is considered to be the addition compound of **7** with methylamine.

A possible mechanism of the new reaction is suggested with a step involving a primary thioamide formation, based on the analogies [11]. This has been confirmed by the synthesis of **9** by the same procedure, starting from primary thioamide **8** where two thioamide functionalities are simultaneously attacked by two methylamine molecules (scheme 4). The intramolecular hydrogen bonding interaction likely stabilizes hydrochloride salt **9**. Interestingly, it was not readily hydrolyzed by acid to an amide. The analysis of the chemical shifts can determine intramolecular hydrogen bond character: **6f** (10.12 ppm), free base of **9** (10.09 ppm), **9** (10.48 ppm). Structures **6f** and **9** show the hydrogen bond between the thymine O2 oxygen and the hydrogen atom on a neighboring thioamide residue. The general procedure [17] with the Lawesson's reagent was applied for the preparation of 1-(3-cyanopropyl)-4-thiothymine (**7**), along with thioamide **8**.

In summary, new methods and synthetic uses of primary thioamides and cyclic thioamides are presented. It has been shown that the procedures are profitable for the synthesis of



SCHEME 4

secondary thioamides, highly selective but time consuming. Perhaps microwaves may improve the reaction time. The use of 33% methylamine in absolute ethanol has made them possible to carry out the reactions in normal vessels rather than autoclaves or sealed tubes. The new intramolecular thiation of 1-(3-cyanopropyl)-4-thiothymine proceeds at room temperature with the migration of the H_2S molecule. The stability of the product over hydrogen bonding is an important driving force for the reaction. A primary thioamide may have been an intermediate, since 1-[3-(thiocarbamoyl)propyl]-4-thiothymine gave the same product on treatment with methylamine.

3. Experimental

Melting points are uncorrected and were determined by using a Boetius melting-point apparatus. NMR spectra were recorded on a Varian 300 Gemini spectrometer in DMSO-d_6 solutions with TMS as a standard and IR spectra on a Bruker 113v FT-IR spectrometer (ν_{max}, KBr discs). High resolution mass spectra were obtained using an AMD 402 or 602 mass spectrometer in the EI or FAB mode, respectively. TLC was carried out on Merck silica gel $60F_{254}$ plates (0.25 mm thickness). All final samples were dried first in an oven at 120 °C and then stored in a vacuum desiccator over phosphorus pentoxide. 33% Methylamine in absolute ethanol, α-bromo-*m*-tolunitrile, and thiobenzamide (**5a**) were available from Aldrich. 20–22% Ammonium sulfide solution in water and 33% dimethylamine in absolute ethanol were purchased from Fluka. The Lawesson's reagent was easily prepared from anisole and phosphorus pentasulfide directly before use [18, 19]. 4-Cyanobenzamides **1a–b** [20], 1-(cyanomethyl)uracil (**1c**) [8, 21], 1-(2-cyanoethyl)thymine (**1 g**) [21, 22], 1-(3-cyanopropyl)thymine (**3**) [21], and 1-(2-cyanoethyl)cytosine (**1e**) [22] were obtained under comparable conditions to the literature. The known primary thioamides **5b–f** have melting points in agreement with the literature [9, 23–26].

3.1 *Preparation of starting 1-substituted cytosines*

The reaction of cytosine (3.6365 g, 0.0327 mol) with chloroacetonitrile (3 mL) in 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 20 mL) was carried out in the general manner which was described previously for thymine [21]. The major modification was in use of silylated unprotected cytosine in excess HMDS. Usually, such products were obtained by reaction of the appropriate N^4-acyl derivatives [27, 28]. The crude product was purified by crystallization from boiling water (100 mL). A second crop of **1d** was obtained by further concentration of the filtrate.

3.1.1 (1-Cytosinyl)acetonitrile (1d). 89%; mp > 300 °C; ^{1}H NMR δ (ppm): 4.75 (s, 2H, CH_2), 5.75 (d, 1H, $J = 7.4$ Hz, C5*H*), 7.34 (s, 1H, N*H*), 7.37 (s, 1H, N*H*), 7.65 (d, 1H, $J = 7.4$ Hz, C6*H*); ^{13}C NMR δ (ppm): 36.8, 94.9, 116.5, 145.0, 155.0, 166.4; HRMS (EI): $M^{+\cdot}$, found 150.0534. $C_6H_6N_4O$ requires 150.0542.

3.1.2 3-(5-Fluorocytosine-1-yl)propionitrile (1f). This compound was synthesized by the literature method [22] from 5-fluorocytosine (1 g, 0.0078 mol) and acrylonitrile (3 mL) in 50% aqueous pyridine (34 mL). 58%; mp 260–261 °C (lit. [29, 30] 208–210 °C); ^{1}H NMR δ (ppm): 2.91 (t, 2H, $J = 6.6$ Hz, CH_2), 3.87 (t, 2H, $J = 6.6$ Hz, CH_2), 7.54 (s, 1H, N*H*), 7.78 (s, 1H, N*H*$\cdots$F, one hydrogen of the NH_2 group is subjected to hydrogen bonding), 8.02

(d, 1H, $J = 6.6$ Hz, C6*H*); ^{13}C NMR δ (ppm): 16.6, 44.6, 118.3, 130.2 (d, $J = 30.9$ Hz), 135.4 (d, $J = 240.1$ Hz), 153.5, 157.6 (d, $J = 13.0$ Hz); HRMS (EI): $M^{+\cdot}$, found 182.0611. $C_7H_7FN_4O$ requires 182.0604.

3.1.3 α-(1-Thyminyl)-*m*-tolunitrile (1 h). This nitrile was prepared by the reaction of silylated thymine with α-bromo-*m*-tolunitrile (8.9382 g, 0.0456 mol) in an oil bath at 130 °C for 18 h, starting from thymine (5 g, 0.04 mol) and HMDS (20 mL). The cooled reaction mixture was treated with methanol and diethyl ether. The product was filtered, washed with isopropanol and water. 95%; mp 204 °C; ^{1}H NMR δ (ppm): 1.77 (d, 3H, $J = 1.1$ Hz, CH_3), 4.90 (s, 2H, CH_2), 7.50–7.90 (m, 4H, C_6H_4), 7.68 (d, 1H, $J = 1.1$ Hz, C6*H*), 11.38 (s, 1H, N3*H*); ^{13}C NMR δ (ppm): 12.1, 49.6, 109.4, 111.6, 118.7, 130.0, 131.2, 131.5, 132.5, 138.7, 141.2, 151.1, 164.4; HRMS (EI): $M^{+\cdot}$, found 241.0860. $C_{13}H_{11}N_3O_2$ requires 241.0851.

3.2 *General procedure for the synthesis of thioamide 2*

A mixture of nitrile **1** (0.01 mol), 20–22% ammonium sulfide solution in water (4 mL), and pyridine (10 mL) was occasionally shaken for two months at room temperature. After removal of pyridine *in vacuo* the remaining residue was washed with water. The pure compound **2** was obtained by recrystallization from the following solvents: methanol (**2a**), methanol-chloroform (**2b**), or boiling water (**2c–h**). After standing for about one year in a stoppered flask, the solution of **3** (3.864 g, 0.02 mol) in 20–22% $(NH_4)_2S$ in water (7.5 mL) and pyridine (7.5 mL) was exposed to a blast of air to remove the solvents and the residue allowed to dry. On acidifying with 1 N hydrochloric acid, salt **4** was obtained after crystallization from methanol.

3.2.1 4-(*N*-Methylcarbamoyl)thiobenzamide (2a). 92%; mp 209–210 °C; IR ν (cm^{-1}): 3380, 3254, 3107, 1673, 1631, 1568, 1545, 1503, 1428, 1398, 1322, 1309, 1272, 1162, 1138; ^{1}H NMR δ (ppm): 2.80 (d, 3H, $J = 4.4$ Hz, NCH_3), 7.84 (d, 2H, $J = 8.2$ Hz), 7.92 (d, 2H, $J = 8.8$ Hz), 8.55 (br q, 1H, $J = 4.9$ Hz, N*H*CO), 9.61 (s, 1H, N*H*CS), 10.01 (s, 1H, N*H*CS); ^{13}C NMR δ (ppm): 26.3, 126.7, 127.2, 136.5, 141.5, 165.9, 199.4; LRMS (EI): 194 (100), 164 (72), 137 (21), 136 (10), 119 (9); HRMS (EI): $M^{+\cdot}$, found 194.0510. $C_9H_{10}N_2OS$ requires 194.0514.

3.2.2 4-(*N,N*-Dimethylcarbamoyl)thiobenzamide (2b). 95%; mp 237–238 °C; IR ν (cm^{-1}): 3254, 3111, 1664, 1617, 1607, 1517, 1481, 1424, 1411, 1399, 1315, 1295, 1265, 1224, 1137; ^{1}H NMR δ (ppm): 2.90 (s, 3H, NCH_3), 2.99 (s, 3H, NCH_3), 7.44 (d, 2H, $J = 8.5$ Hz), 7.92 (d, 2H, $J = 8.5$ Hz), 9.61 (s, 1H, N*H*CS), 10.00 (s, 1H, N*H*CS); ^{13}C NMR δ (ppm): 34.7, 38.9, 126.5, 127.3, 138.9, 140.0, 169.4, 199.5; LRMS (EI): 208 (80), 164 (100), 137 (25), 130 (18), 119 (9); HRMS (EI): $M^{+\cdot}$, found 208.0670. $C_{10}H_{12}N_2OS$ requires 208.0670.

3.2.3 (1-Uracilyl)thioacetamide (2c). 89%; mp 231–232 °C; IR ν (cm^{-1}): 3263, 3119, 3026, 2926, 2875, 2835, 2816, 1697, 1661, 1622, 1461, 1426, 1395, 1355, 1336; ^{1}H NMR δ (ppm): 4.54 (s, 2H, CH_2), 5.56 (d, 1H, $J = 7.7$ Hz, C5*H*), 7.51 (d, 1H, $J = 8.0$ Hz, C6*H*), 9.43 (s, 1H, N*H*CS), 9.77 (s, 1H, N*H*CS), 11.24 (s, 1H, N3*H*); ^{13}C NMR δ (ppm): 55.5, 100.5, 146.8, 151.0, 164.1, 201.2; LRMS (EI): 185 (100), 168 (80), 126 (56), 82 (60), 74 (20); HRMS (EI): $M^{+\cdot}$, found 185.0253. $C_6H_7N_3O_2S$ requires 185.0259.

3.2.4 (1-Cytosinyl)thioacetamide (2d). 91%; mp > 300 °C; IR ν (cm^{-1}): 3465, 3235, 3037, 2963, 2925, 1659, 1613, 1526, 1502, 1467, 1388, 1333, 1312, 1281, 1262; ^{1}H NMR δ (ppm): 4.49 (s, 2H, CH_2), 5.64 (d, 1H, J = 7.4 Hz, C5*H*), 6.99 (br s, 1H, N*H*), 7.08 (br s, 1H, N*H*), 7.45 (d, 1H, J = 7.4 Hz, C6*H*), 9.33 (s, 1H, CSN*H*), 9.65 (s, 1H, CSN*H*); ^{13}C NMR δ (ppm): 57.0, 93.0, 147.2, 155.7, 166.3, 202.4; LRMS (EI): 184 (50), 151 (100), 125 (67), 111 (27), 96 (40); HRMS (EI): $M^{+\cdot}$, found 184.0413. $C_6H_8N_4OS$ requires 184.0419.

3.2.5 3-(1-Cytosinyl)thiopropionamide (2e). 88%; mp 303–305 °C; IR ν (cm^{-1}): 3373, 3327, 3271, 3109, 1662, 1623, 1597, 1523, 1481, 1441, 1430, 1387, 1375, 1357, 1289; ^{1}H NMR δ (ppm): 2.80 (t, 2H, J = 6.7 Hz, CH_2), 3.97 (t, 2H, J = 6.7 Hz, CH_2), 5.60 (d, 1H, J = 7.1 Hz, C5*H*), 6.98 (br s, 1H, N*H*), 7.04 (br s, 1H, N*H*), 7.52 (d, 1H, J = 7.1 Hz, C6*H*), 9.32 (s, 1H, N*H*CS), 9.48 (s, 1H, N*H*CS); ^{13}C NMR δ (ppm): 42.5, 48.4, 93.0, 146.3, 155.7, 166.0, 204.8; LRMS (EI): 198 (3), 164 (6), 138 (7), 111 (60), 28 (100); HRMS (EI): $M^{+\cdot}$, found 198.0572. $C_7H_{10}N_4OS$ requires 198.0575.

3.2.6 3-(5-Fluorocytosin-1-yl)thiopropionamide (2f). 73%; mp 214–216 °C; IR ν (cm^{-1}): 3420, 3315, 3289, 3116, 2955, 1684, 1613, 1521, 1472, 1443, 1423, 1388, 1363, 1343, 1283; ^{1}H NMR δ (ppm): 2.81 (t, 2H, J = 6.9 Hz, CH_2), 3.95 (t, 2H, J = 6.7 Hz, CH_2), 7.60 (br s, 1H, N*H*), 7.80 (br s, 1H, N*H*), 7.84 (d, 1H, J = 6.9 Hz, C6*H*), 9.32 (s, 1H, CSN*H*), 9.50 (s, 1H, CSN*H*); ^{13}C NMR δ (ppm): 42.1, 48.3, 130.8 (d, J = 30.9 Hz, *C*6H), 135.1 (d, J = 240.5 Hz, *C*5F), 153.9, 157.5 (d, J = 13.7 Hz, *C*4NH_2), 204.6; LRMS (EI): 216 (3), 156 (5), 130 (13), 87 (8), 28 (100); HRMS (EI): $M^{+\cdot}$, found 216.0498. $C_7H_9FN_4OS$ requires 216.0481.

3.2.7 3-(1-Thyminyl)thiopropionamide (2 g). 96%; mp 203–206 °C; IR ν (cm^{-1}): 3463, 3392, 3344, 3212, 3079, 3018, 2930, 2893, 2826, 1684, 1650, 1636, 1521, 1480, 1466; ^{1}H NMR δ (ppm): 1.73 (d, 3H, J = 1.1 Hz, CH_3), 2.80 (t, 2H, J = 6.7 Hz, CH_2), 3.97 (t, 2H, J = 6.9 Hz, CH_2), 7.45 (d, 1H, J = 1.1 Hz, C6*H*), 9.33 (s, 1H, CSN*H*), 9.53 (s, 1H, CSN*H*), 11.25 (s, 1H, N3*H*); ^{13}C NMR δ (ppm): 12.0, 42.5, 47.0, 108.0, 141.7, 150.7, 164.4, 204.3; LRMS (EI): 213 (52), 152 (6), 126 (28), 96 (38), 88 (100); HRMS (EI): $M^{+\cdot}$, found 213.0568. $C_8H_{11}N_3O_2S$ requires 213.0572.

3.2.8 α-(1-Thyminyl)-*m*-thiotoluamide (2 h). 95%; mp 222–223 °C; IR ν (cm^{-1}): 3401, 3290, 3191, 3129, 2986, 2832, 1689, 1665, 1636, 1475, 1443, 1431, 1387, 1357, 1322; ^{1}H NMR δ (ppm): 1.76 (d, 3H, J = 0.8 Hz, CH_3), 4.88 (s, 2H, CH_2), 7.40 (d, 1H, J = 4.7 Hz), 7.41 (d, 1H, J = 3.0 Hz), 7.64 (d, 1H, J = 1.4 Hz, C6*H*), 7.76 (t, 1H, J = 4.5 Hz), 7.81 (s, 1H), 9.55 (s, 1H, CSN*H*), 9.93 (s, 1H, CSN*H*), 11.37 (s, 1H, N3*H*); ^{13}C NMR δ (ppm): 12.0, 49.9, 109.1, 126.2, 126.6, 128.3, 130.0, 136.8, 140.0, 141.2, 151.0, 164.3, 199.9; LRMS (EI): 275 (85), 241 (36), 151 (37), 150 (36), 116 (100); HRMS (EI): $M^{+\cdot}$, found 275.0708. $C_{13}H_{13}N_3O_2S$ requires 275.0729.

3.2.9 4-(1-Thyminyl)butyramidine (4). 18%; mp > 300 °C; IR ν (cm^{-1}): 3320, 3146, 3039, 2819, 1705, 1675, 1516, 1478, 1446, 1427, 1390, 1370, 1214, 1106, 994; ^{1}H NMR δ (ppm): 1.76 (s, 3H, CH_3), 1.92 (quintet, 2H, J = 7.3 Hz, $CH_2CH_2CH_2$), 2.38 (t, 2H, J = 8.1 Hz, CH_2), 3.68 (t, 2H, J = 6.6 Hz, NCH_2), 7.52 (d, 1H, J = 1.2 Hz, C6*H*), 8.53 (br s, 2H, 2 N*H*, inside protons), 8.88 (br s, 2H, 2 N*H*, outside protons), 11.29 (br s, 1H, N3*H*); ^{13}C

NMR δ (ppm): 12.0, 25.9, 29.2, 46.3, 108.7, 141.3, 151.0, 164.3, 169.9; HRMS (FAB): MH^+, found 211.1180. $C_9H_{15}N_4O_2$ requires 211.1195.

3.3 *General procedure for the synthesis of N-methylthioamide 6*

Primary thioamide **5** (0.005 mol) was dissolved in 33% methylamine in absolute ethanol (10 mL) and the solution allowed to stand for three days at room temperature until the substrate was consumed, as followed by TLC, and then the solution was concentrated in vacuo. The oily residue was solidified upon treatment of ice-water or keeping the flask in the refrigerator until encrustation occurred to give pure sample **6**. It can be also purified by column chromatography on silica gel (100–200 mesh, 18:1 chloroform–methanol) and recrystallized from aqueous isopropanol. Considerable recovery of starting material **5a** was observed when the reaction was carried out in 33% dimethylamine in absolute ethanol under conditions analogous to those used above.

3.3.1 ***N*-Methyl(thiobenzamide) (6a).** 92%; mp 77–78 °C (lit. [26] 79 °C); IR ν (cm^{-1}): 3315, 3063, 2997, 2950, 2923, 1539, 1489, 1457, 1437, 1394, 1358, 1317, 1287, 1240, 1045; ^{1}H NMR δ (ppm): 3.15 (d, 3H, $J = 4.7$ Hz, CH_3), 7.36–7.53 (m, 3H), 7.78 (d, 2H, $J = 8.2$ Hz), 10.29 (br s, 1H, N*H*); ^{13}C NMR δ (ppm): 33.6, 127.2, 128.1, 130.7, 141.0, 197.6; LRMS (EI): 151 (100), 150 (72), 121 (68), 118 (20), 117 (16); HRMS (EI): $M^{+\cdot}$, found 151.0447. C_8H_9NS requires 151.0456.

3.3.2 ***N*-Methyl(thio-*p*-toluamide) (6b).** 94%; mp 53–55 °C (lit. [26] 55 °C); IR ν (cm^{-1}): 3309, 2952, 2924, 2855, 1608, 1540, 1506, 1443, 1406, 1377, 1355, 1349, 1315, 1286, 1242; ^{1}H NMR δ (ppm): 2.33 (s, 3H, C*H*$_3$), 3.14 (d, 3H, $J = 4.7$ Hz, NCH_3), 7.22 (d, 2H, $J = 8.2$ Hz), 7.72 (d, 2H, $J = 8.2$ Hz), 10.19 (br s, 1H, N*H*); ^{13}C NMR δ (ppm): 20.8, 33.4, 127.1, 128.5, 138.0, 140.6, 197.1; LRMS (EI): 165 (100), 164 (61), 150 (14), 135 (62), 132 (20); HRMS (EI): $M^{+\cdot}$, found 165.0625. $C_9H_{11}NS$ requires 165.0612.

3.3.3 ***N*-Methyl(thio-4-bromobenzamide) (6c).** 92%; mp 135–136 °C; IR ν (cm^{-1}): 3334, 3012, 2965, 2925, 1585, 1564, 1537, 1483, 1446, 1394, 1360, 1352, 1302, 1273, 1255, 593; ^{1}H NMR δ (ppm): 3.14 (d, 3H, $J = 4.4$ Hz, C*H*$_3$), 7.64 (d, 2H, $J = 8.8$ Hz), 7.73 (d, 2H, $J = 8.8$ Hz), 10.38 (br s, 1H, N*H*); ^{13}C NMR δ (ppm): 33.5, 124.3, 129.1, 131.0, 139.8, 195.9; LRMS (EI): 232 (14), 231 (100), 230 (94), 229 (97), 228 (82). HRMS (EI): $M^{+\cdot}$, found 228.9550 and 230.9556. $C_8H_8^{79}BrNS$ and $C_8H_8^{81}BrNS$ require 228.9561 and 230.9540, appropriately.

3.3.4 ***N*-Methyl(thiophenylacetamide) (6d).** 89%; mp 61–62 °C (lit. [26] 62.5–63 °C); IR ν (cm^{-1}): 3214, 3065, 2963, 2928, 1549, 1538, 1494, 1467, 1451, 1439, 1418, 1383, 1366, 1295, 1284; ^{1}H NMR δ (ppm): 2.96 (d, 3H, $J = 4.4$ Hz, C*H*$_3$), 3.89 (s, 2H, C*H*$_2$), 7.20–7.40 (m, 5H), 10.21 (s, 1H, N*H*); ^{13}C NMR δ (ppm): 32.5, 51.2, 126.6, 128.2, 128.7, 137.5, 201.5; LRMS (EI): 165 (100), 134 (11), 117 (8), 92 (32), 91 (37); HRMS (EI): $M^{+\cdot}$, found 165.0612. $C_9H_{11}NS$ requires 165.0612.

3.3.5 ***N*-Methyl(thio-3,4-dimethoxyphenylacetamide) (6e).** 88%; mp 128–130 °C (lit. [31, 32] 130 °C); IR ν (cm^{-1}): 3313, 3031, 2992, 2956, 2935, 2838, 1608, 1592, 1553, 1520,

1465, 1451, 1438, 1421, 1369; ^{1}H NMR δ (ppm): 2.94 (d, 3H, $J = 4.4$ Hz, CH_3), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.81 (s, 2H, CH_2), 6.84 (d, 1H, $J = 1.7$ Hz), 6.86 (s, 1H), 6.97 (d, 1H, $J = 1.7$ Hz), 10.08 (br s, 1H, NH); ^{13}C NMR δ (ppm): 32.5, 50.9, 55.4, 55.5, 111.7, 112.8, 120.8, 129.7, 147.7, 148.4, 201.9; LRMS (EI): 225 (100), 194 (22), 179 (4), 151 (59), 137 (27); HRMS (EI): $M^{+\cdot}$, found 225.0828. $C_{11}H_{15}NO_2S$ requires 225.0824.

3.3.6 ***N*-Methyl(1-thyminyl)thioacetamide (6f).** 90%; mp 308 °C (with sublimation); IR ν (cm^{-1}): 3268, 3141, 3092, 2986, 2831, 1683, 1571, 1488, 1475, 1433, 1427, 1398, 1384, 1360, 1334; ^{1}H NMR δ (ppm): 1.76 (d, 3H, $J = 1.1$ Hz, C5CH_3), 2.99 (s, 3H, NCH_3), 4.58 (s, 2H, CH_2), 7.42 (d, 1H, $J = 1.2$ Hz, C6H), 10.12 (br s, 1H, CSNH···O = C2, no coupling with the CH_3 protons), 11.26 (br s, 1H, N3H); ^{13}C NMR δ (ppm): 12.0, 32.3, 56.0, 108.1, 142.4, 151.0, 164.6, 197.2; LRMS (EI): 213 (100), 182 (36), 140 (70), 127 (11), 111 (7); HRMS (EI): $M^{+\cdot}$, found 213.0584. $C_8H_{11}N_3O_2S$ requires 213.0572.

3.4 *Reaction of 4-thiothymine 7 or 8 with methylamine*

A solution of nitrile **3** (20 g, 0.1035 mol) and the Lawesson's reagent (46 g, 0.1137 mol) in dry pyridine (100 mL) was heated under reflux with stirring for 2 hours. The solution was concentrated by evaporation under reduced pressure and the residue then triturated with excess water. The resulting crude solid contained the main product, along with traces of contaminants. After purification by repeated recrystallizations from water and methanol, the yellow needles of **7** and yellow powder of **8** were thus obtained. The presence of single products was shown by TLC (18:1 $CHCl_3$–MeOH).

3.4.1 1-(3-Cyanopropyl)-4-thiothymine (7). 63%; mp 176–177 °C; IR ν (cm^{-1}): 3182, 3073, 3053, 2971, 2958, 2929, 2252, 1685, 1635, 1486, 1462, 1439, 1382, 1358, 1351; ^{1}H NMR δ (ppm): 1.93 (quintet, 2H, $J = 7.0$ Hz, CH_2), 1.95 (d, 3H, $J = 0.9$ Hz, CH_3), 2.56 (t, 2H, $J = 7.2$ Hz, CH_2CN), 3.75 (t, 2H, $J = 7.0$ Hz, NCH_2), 7.69 (d, 1H, $J = 1.0$ Hz, C6H), 12.67 (s, 1H, N3H); ^{13}C NMR δ (ppm): 13.8, 16.7, 24.2, 47.1, 117.2, 120.0, 138.8, 148.5, 190.5; LRMS (EI): 209 (100), 169 (5), 156 (4), 142 (4), 126 (3); HRMS (EI): $M^{+\cdot}$, found 209.0623. $C_9H_{11}N_3OS$ requires 209.0623.

3.4.2 1-[3-(Thiocarbamoyl)propyl]-4-thiothymine (8). 12%; mp 200–201 °C; IR ν (cm^{-1}): 3308, 3136, 2955, 2920, 1714, 1646, 1623, 1474, 1451, 1421, 1378, 1354, 1288, 1239, 1136; ^{1}H NMR δ (ppm): 1.95 (d, 3H, $J = 0.8$ Hz, CH_3), 2.00 (quintet, 2H, $J = 7.6$ Hz, CH_2), 2.48 (t, 2H, $J = 6.0$ Hz, CH_2CS), 3.71 (t, 2H, $J = 7.0$ Hz, NCH_2), 7.69 (d, 1H, $J = 1.1$ Hz, C6H), 9.21 (s, 1H, CSNH), 9.42 (s, 1H, CSNH), 12.66 (s, 1H, N3H); ^{13}C NMR δ (ppm): 16.6, 27.8, 40.9, 47.5, 117.2, 139.1, 148.5, 190.6, 207.0; LRMS (EI): 243 (100), 209 (30), 182 (6), 169 (71), 156 (15); HRMS (EI): $M^{+\cdot}$, found 243.0495. $C_9H_{13}N_3OS_2$ requires 243.0500.

Compound **9** was prepared by two alternative methods, one involves use of **7**, and the another uses **8** as the starting material. Thioamide **8** (0.5 g, 0.0021 mol) was dissolved in 33% methylamine in absolute ethanol (10 mL) and the solution was kept one month at room temperature in a stoppered flask with occasional shaking of the reaction vessel. After this period, the reaction mixture showed one UV spot corresponding to a free base of **9** (27:6:1 $CHCl_3$-MeOH-25% NH_4OH). The latter was evaporated to dryness, redissolved in isopropanol, acidified with isopropanolic hydrogen chloride, and left overnight in the refrigerator. The precipitate was collected by filtration and recrystallized from isopropanol. The same compound was obtained

by similar treatment of **7** (82%). After the reaction was complete, the product was acidified, forming stabilized hydrochloride salt **9**. No intermediate product, containing the unreacted cyano group, was found in the isopropanolic solution of the free base by using TLC analysis. The outcome is consistent with an intramolecular nature of the reaction.

3.4.3 *N*-Methyl-4-(N^4,5-dimethylcytosin-1-yl)thiobutyramide hydrochloride (9). 74%; mp 198–201 °C; IR ν (cm^{-1}): 3183, 3117, 2978, 2946, 2889, 2820, 1705, 1661, 1626, 1559, 1476, 1457, 1442, 1370, 1347; ^{1}H NMR δ (ppm): 1.98 (s, 3H, CH_3), 2.05 (quintet, 2H, $J = 7.2$ Hz, CH_2), 2.62 (t, 2H, $J = 7.4$ Hz, CH_2CS), 2.91 (d, 3H, $J = 4.4$ Hz, $CSNHCH_3$), 3.01 (d, 3H, $J = 4.9$ Hz, NCH_3), 3.77 (t, 2H, $J = 6.7$ Hz, NCH_2), 7.91 (s, 1H, C6*H*), 9.71 (br q, 1H, $J = 4.9$ Hz, cytosine N*H*CH_3), 10.48 (br q, 1H, $J = 4.2$ Hz, CSN*H*CH_3), 12.33 (br s, 1H, N3*H*, offset: 3.1 ppm; this broadening can be explained by a substantial electrostatic interaction with the thiocarbamoyl function); ^{13}C NMR δ (ppm): 12.9, 27.7, 29.6, 32.2, 41.0, 48.0, 101.8, 144.3, 148.3, 157.5, 202.4. Free base of **9.** IR ν (cm^{-1}): 3223, 3063, 2933, 2864, 1666, 1623, 1558, 1511, 1472, 1440, 1419, 1397, 1383, 1340, 1206; ^{1}H NMR δ (ppm): 1.82 (d, 3H, $J = 0.7$ Hz, C5CH_3), 1.94 (quintet, 2H, $J = 7.3$ Hz, $CH_2CH_2CH_2$), 2.51 (t, 2H, $J = 7.7$ Hz, CH_2CS), 2.78 (d, 3H, $J = 4.7$ Hz, CH_3NH), 2.94 (d, 3H, $J = 4.5$ Hz, CH_3NH), 3.63 (t, 2H, $J = 7.0$ Hz, N1CH_2), 7.05 (br q, 1H, $J = 4.5$ Hz, CH_3N*H*), 7.35 (d, 1H, $J = 0.9$ Hz, C6*H*), 10.09 (br s, 1H, CSN*H*$\cdots$O = C2); ^{13}C NMR δ (ppm): 12.7, 27.6, 28.7, 32.3, 41.6, 47.4, 100.9, 141.8, 155.7, 163.2, 202.9; LRMS (EI): 254 (43), 239 (4), 180 (18), 166 (28), 140 (100); HRMS (EI): $M^{+\cdot}$, found 254.1201. $C_{11}H_{18}N_4OS$ requires 254.1201.

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