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Syntheses of N-Substituted Thymine Thioacetamides. A Novel Approach to *Site* Selective Acylation of Diaminoalkanes

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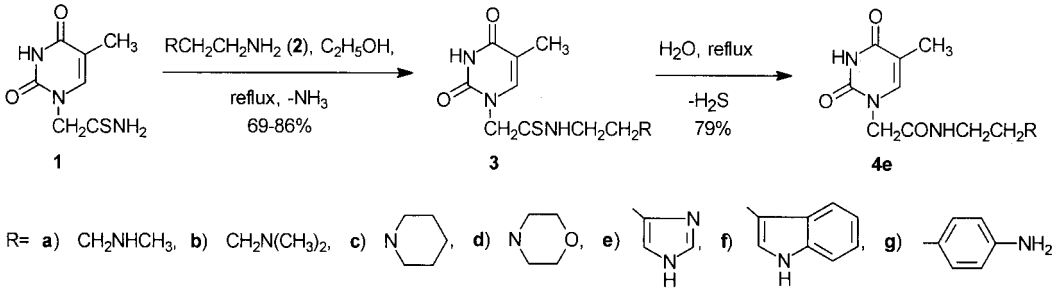
Abstract—A new series of N-substituted thiocarbamoyl derivatives containing histamine, tryptamine, and other moieties having at least one amino group attached to an aliphatic chain, has been synthesized from (1-thyminyl)thioacetamide in good isolated yields (69–86%). *N*-[2-(4-Imidazolyl)ethyl](1-thyminyl)thioacetamide was hydrolyzed to its amide on prolonged heating in water. Ammonium sulfide (20–22% solution in water) has found interesting new applications in the efficient synthesis of *N*-[2-(3-indolyl)ethyl](1-thyminyl)thioacetamide and *site* selective acylation of diaminoalkanes, starting directly from nitriles.

Introduction

The search for new thymine chemotherapeutical agents, has stimulated tremendous efforts towards the synthesis of nucleoside analogues over the past decade. In general, these compounds have been designed as antimetabolites through isosteric substitution or through modification of the sugar moiety.[1] Considerable interest has been focused on different sulfur analogues.[2] Hitherto, no report has been encountered on the preparation of N-substituted thymine thioacetamides which would deal with a study of the Wallach reaction.

Results and discussion

The preparation of the new title compounds is outlined in Scheme 1. The substitution of one amino group by another one to form N-substituted thioamides was used for synthetic purposes.[3] The corresponding products **3** were obtained by refluxing readily available (1-thyminyl)thioacetamide (**1**) with a primary amine **2** in ethanol by employing approximately equimolar quantities of the reactants. The bases used included several mono-substituted aliphatic diamines, histamine, tryptamine, and 4-aminophenethylamine. Purification was effected by recrystallization from methanol or water. The products were isolated as free bases or their hydrochloride salts. N-substituted thioamides can be readily hydrolyzed by the action of bases.[4] *N*-[2-(4-Imidazolyl)-ethyl](1-thyminyl)thioacetamide (**3e**) lost sulfur by itself, simply by heating in water for an extended time (an imidazole residue as a desulfurizing agent). Therefore, care must be taken when crystallizing the products having basic groups from water. It is of interest to note that thioacetamide **3a** did not show any tendency to cyclize into a *N*-methyltetrahydropyrimidine derivative, even after long refluxing. As will be shown below, a simple and general procedure is efficient for the formation of **3**.



Scheme 1.

Keywords: Wallach reaction; thioamides; amides; uracils.

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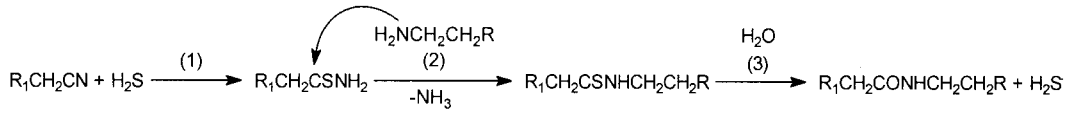
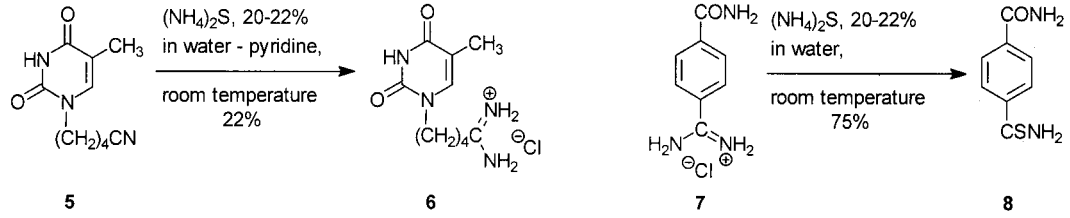


Scheme 2. (1) Addition; (2) substitution of the amino group; (3) hydrolysis.



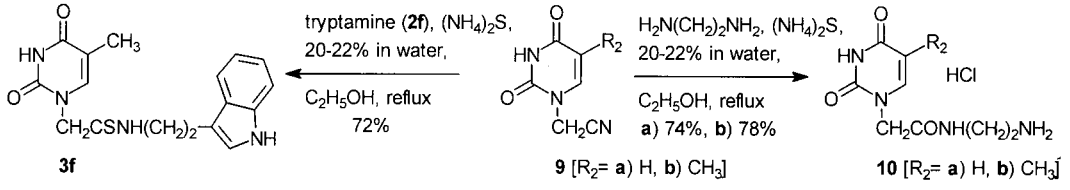
Scheme 3.

In contrast to literature data,[5] the above examples support a general mechanism. Treatment of a nitrile with one equivalent of ammonium sulfide yields a primary thioamide,[6,7] which on successive treatment with an appropriate primary amine affords N-substituted thioamide. The formation of products is dependent on the nature of the N-substituents. For R=NH_2 the amide was found to be the only product and N-substituted thioamide was only an intermediate in the reaction, the elimination of hydrogen sulfide was performed by refluxing in aqueous solution (see a reaction sequence in Scheme 2. It has been suggested previously that the reaction proceeds via a N-substituted simple amidine intermediate (instead of a N-substituted thioamide) followed by a nucleophilic substitution of the mercapto group. This suggestion was supported by the fact that simple amidines can be obtained sometimes by treating some nitriles or thioamides with ammonium sulfide or amines, respectively.[8] 1-(4-Amidinobutyl)thymine (**6**) was also isolated from a mixture of 1-(4-cyanobutyl)-thymine (**5**) and an excess of aqueous ammonium sulfide-pyridine after prolonged standing at room temperature. However, the syntheses of **3**, **10**, and **12** require heating under reflux and therefore, no simple amidine intermediate was observed. Formation of 4-(thiocarbamoyl)benzamide (**8**) from 4-amidinobenzamide (**7**) and aqueous $(NH_4)_2S$ even at room temperature indicates why no evidence of the simple amidine intermediate was obtained (Scheme 3). This result is in accord with previous observations.[9]

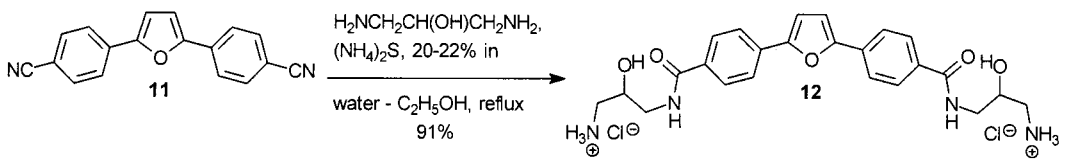
Commercially available 20–22% ammonium sulfide aqueous solution has already found applications for the preparation of several unsubstituted thioamides.[6,7] As will be shown below in Scheme 4, *N*-[2-(3-indolyl)-ethyl](1-thyminyl)thioacetamide (**3f**) can be readily prepared by direct reaction of a nitrile with a primary monoamine in the presence of small excess of $(NH_4)_2S$ in water-ethanol. This procedure is an example of the synthesis of *N*-substituted thioamides by the use of nitriles under aqueous conditions. Other literature reactions took the same course under anhydrous conditions.[10]

Unfortunately, the above new method offers no advantage for the preparation of all products **3**. When a basic group was attached to the N-substituent, self-desulfurization occurred under the reaction conditions. The amide **10** resulted in good yield from a *site* selective reaction of **9** with ethylenediamine in ethanol-ammonium sulfide, 20–22% solution in water. Such a reaction was to be expected in view of an earlier published work.[5] It has recently been shown that a similar reaction proceeded under anhydrous conditions and afforded cyclized amidines upon substitution and cyclization (N-substituted thioamide intermediate was involved in the reaction).[11,12] Syntheses from (1-uracilyl and 1-thyminyl)acetonitriles (**9**) are presented in Scheme 4.

The application of the $(NH_4)_2S$-acylation method was



Scheme 4.



Scheme 5.

extended for the preparation of a new dicationic diaryl furan molecule. 2,5-Bis{4-[*N*-(3-amino-2-hydroxypropyl)carbamoyl]phenyl}furan dihydrochloride (**12**) was obtained in excellent 91% yield in a one-step reaction starting from 2,5-bis(4-cyanophenyl)furan (**11**) and 1,3-diamino-2-hydroxypropane (Scheme 5).

Conclusion

In conclusion, the procedures presented appear to offer considerable utility for the simple synthesis of a new series of 1-substituted thymines from readily available substrates by using the Wallach reaction. An alternative preparative route was available for some of these products. (1-Uracilyl and 1-thyminyl)acetonitriles found here new applications as *site* selective acylating agents for the synthesis of monosubstituted diaminoalkanes. The procedure presented was particularly advantageous in the preparation of the more substituted diamide derivative. The products of these reactions are valuable for the general mechanism. An analytical reagent-$(NH_4)_2S$, 20–22% solution in water, proved to be a useful tool in organic syntheses.

Experimental

Melting points are uncorrected and were determined by using Boetius melting-point apparatus. NMR spectra were recorded on Varian Gemini 300 MHz (75.5 MHz for ^{13}C) spectrometer in DMSO-d_6 with TMS as a standard (unless indicated otherwise), while IR spectra on a FT-IR Bruker 113 V spectrometer. High resolution mass spectra were made in AMD 402 or 602 mass spectrometers by using EI or FAB modes, respectively. Thin-layer chromatography was performed with Merck silica gel $60F_{254}$ glass plates (0.25 mm thickness) in three solvent systems: 44:8:1, 11:4:1, or 7:5:2 $CHCl_3$–CH_3OH–NH_4OH (chloroform was distilled from P_2O_5). All compounds showed a single spot on TLC visualized with UV absorption (254 nm). The primary amines gave a positive reaction with 0.2% ninhydrin ethanolic solution. Amines **2** [**a**) *N*-methylpropanediamine, **b**) 3-(dimethylamino)propylamine, **c**) 1-(2-aminoethyl)piperidine, **d**) 4-(2-aminoethyl)morpholine, **e**) histamine, **f**) tryptamine, **g**) 2-(4-aminophenyl)ethylamine], 1,3-diamino-2-hydroxypropane, ethylenediamine, and 4-amidinobenzamide hydrochloride (**7**) were purchased from Aldrich. Ammonium sulfide, 20-22% solution in water was commercially available from Merck. The following chemicals: (1-thyminyl)thioacetamide (**1**),[6] 1-(4-cyanobutyl)thymine (**5**),[12] (1-uracilyl)acetonitrile (**9a**),[13] (1-thyminyl)acetonitrile (**9b**),[6,14] and 2,5-bis(4-cyanophenyl)furan (**11**)[15] were prepared by known methods. All final samples were dried in a vacuum oven.

General procedure for the synthesis of N-substituted thymine thioacetamides 3

In a typical experiment (1-thyminyl)thioacetamide (**1**, 1 g, 0.0051 mol) was suspended in a solution of a primary amine (**2**, 0.0051 mol) in ethanol (10 mL). The reaction mixture was then heated under reflux with stirring for 18 h under anhydrous conditions. Evolution of ammonia was noticed after the heating had begun. After cooling in the refrigerator, the solid was filtered off, washed with cold water, and recrystallized from hot water (**3e**), methanol (**3b**, **3c**, **3d**, **3f**, **3g**), methanol/2-propanol (**3a**) to afford colourless crystals. The free base **3a** was not cyclized on refluxing for additional twenty hours in ethanol and only the starting material was recovered. **3a** was acidified with 1N hydrochloric acid. The solution was evaporated to dryness and the residue recrystallized from methanol. Product precipitated out on cooling as a white solid.

***N*-[3-(Methylamino)propyl](1-thyminyl)thioacetamide hydrochloride (3a · HCl).** 75%; mp 250–251°C (dec.); δ_H 1.76 (d, 3H, J=0.9 Hz, CH_3), 2.70–2.90 (m, 6H, CH_2CH$_2$NH$^+$H CH_3), 3.32 (t, 2H, J=6.4 Hz, CH$_2$CH_2N), 3.94 (dt, 2H, J=5.8, 5.8 Hz, CSNHCH_2), 4.62 (s, 2H, NCH_2CS), 7.46 (d, 1H, J=1.2 Hz, C6*H*), 10.49 (m, 2H, CSN*H*, intramolecular $(\delta+)$S=C$(\delta-)\cdots\cdots H^+$NHCH$_3$ bonds), 11.29 (br s, 1H, N3*H*); δ_C 11.8, 39.9, 42.2 (double intensity), 53.6, 55.8, 108.1, 142.6, 151.2, 164.8, 199.0; δ_H [D_2O, $(CH_3)_3Si(CH_2)_3SO_3Na$] 1.90 (s, 3H, CH_3), 2.87–3.02 (m, 5 H, CH_2CH$_2$NCH_3), 3.51 (t, 2H, J=6.2 Hz, CH$_2$CH_2N), 4.13 (t, 2H, J=6.2 Hz, CSNHCH_2), 4.75 (s, 2H, NCH_2CS), 7.45 (d, 1H, J=1.1 Hz, C6*H*); δ_C (D_2O, $(CH_3)_3Si(CH_2)_3SO_3Na$) 14.0, 43.0, 45.7, 45.8, 57.4, 59.6, 113.4, 146.0, 154.9, 169.4, 202.0; HRMS (EI): M$^+$, found 270.1156. $C_{11}H_{18}N_4O_2S$ requires 270.1151. The product gave a negative ninhydrin test for primary amine.

***N*-[3-(Dimethylamino)propyl](1-thyminyl)thioacetamide (3b).** 79%; mp 199–202°C (dec.); δ_H 1.69 (quintet, 2H, J=7.0 Hz, CH$_2$CH_2CH$_2$), 1.76 (d, 3H, J=0.8 Hz, CH_3), 2.11 (s, 6H, CH_3NCH_3), 2.25 (t, 2H, J=6.9 Hz, CH$_2$CH_2N), 3.55 (br m, 2H, CSNHCH_2), 4.56 (s, 2H, NCH_2CS), 7.43 (d, 1H, J=1.1 Hz, C6*H*), 10.21 (br s, 1H), 11.29 (br s, 1H, N3*H*); δ_C 12.0, 24.8, 44.1, 45.1, 56.0, 56.8, 107.9, 142.5, 151.0, 164.6, 196.5; HRMS (EI): M$^+$, found 284.1319. $C_{12}H_{20}N_4O_2S$ requires 284.1307.

***N*-[2-(1-Piperidino)ethyl](1-thyminyl)thioacetamide (3c).** 86%; mp 237–238°C (dec.); δ_H 1.37 (m, 2H, piperidine C4*H*), 1.48 (m, 4H, piperidine C3*H* and C5*H*), 1.76 (s, 3H, CH_3), 2.35 (m, 4H, piperidine C2*H* and C6*H*), 2.46 (t, 2H, J=6.9 Hz, CH$_2$CH_2N), 3.63 (t, 2H, J=6.7 Hz, CSNHCH_2), 4.56 (s, 2H, NCH_2CS), 7.41 (d, 1H, J= 1.1 Hz, C6*H*), 10.03 (br s, 1H, CSN*H*), 11.27 (br s, 1H, N3*H*); δ_C 12.0, 24.0, 25.5, 42.8, 53.9, 55.5, 55.8, 107.7, 142.3, 150.7, 164.3, 196.5; HRMS (EI): M$^+$, found 310.1487. $C_{14}H_{22}N_4O_2S$ requires 310.1464.

***N*-[2-(4-Morpholino)ethyl](1-thyminyl)thioacetamide (3d).** 74%; mp 226°C; δ_H 1.76 (d, 3H, J=0.8 Hz, CH_3), 2.39 (m, 4H, morpholine C3*H* and C5*H*), 2.51 (t, 2H, J=6.6 Hz, CH$_2$CH_2N), 3.57 (m, 4H, morpholine C2*H* and C6*H*), 3.66 (dt, 2H, J=6.5, 5.2 Hz, CSNHCH_2), 4.57 (s, 2H, NCH_2CS), 7.42 (d, 1H, J=1.1 Hz, C6*H*), 10.08 (br t, 1H, CSN*H*CH$_2$), 11.27 (br s, 1H, N3*H*); δ_C 12.0, 42.4, 53.2, 55.2, 55.8, 66.1, 107.7, 142.3, 150.7, 164.3, 196.7; HRMS (EI): M$^+$, found 312.1271. $C_{13}H_{20}N_4O_3S$ requires 312.1256.

***N*-[2-(4-Imidazolyl)ethyl](1-thyminyl)thioacetamide (3e).** 77%; mp 245–246°C (dec.); δ_H 1.77 (s, 3H, CH_3), 2.81 (t, 2H, J=7.3 Hz, CH$_2$CH_2C), 3.74 (dt, 2H, J=7.2, 5.2 Hz,

CSNHCH_2), 4.58 (s, 2H, NCH_2CS), 6.85 (s, 1H, imidazole C5*H*), 7.42 (d, 1H, *J*=0.8 Hz, C6*H*), 7.53 (d, 1H, *J*= 1.1 Hz, imidazole C2*H*), 10.31 (br t, 1H, *J*=4.8 Hz, CSN*H*CH_2), 11.30 (s, 1H, N3*H*), 11.87 (br s, 1H, imidazole N*H*); δ_C 12.0, 25.0, 45.3, 55.9, 107.9, 116.8, 134.7 (double intensity), 142.5, 151.0, 164.6, 196.7; HRMS (EI): M^+, found 293.0954. $C_{12}H_{15}N_5O_2S$ requires 293.0946.

***N*-[2-(3-Indolyl)ethyl](1-thyminyl)thioacetamide (3f).** 70%; mp 220–221°C (dec.); δ_H 1.77 (s, 3H, CH_3), 3.01 (t, 2H, *J*=7.4 Hz, CH_2CH_2C), 3.81 (dt, 2H, *J*=7.4, 5.5 Hz, CSNHCH_2), 4.59 (s, 2H, NCH_2CS), 7.00 (dt, 1H, *J*=7.4, 0.8 Hz, indole *H4*), 7.08 (dt, 1H, *J*=7.4, 1.1 Hz, indole *H5*), 7.20 (d, 1H, *J*=2.2 Hz, indole *H2*), 7.35 (d, 1H, *J*=8.0 Hz, indole *H3*), 7.40 (d, 1H, *J*=1.1 Hz, C6*H*), 7.60 (d, 1H, *J*=7.7 Hz, indole *H6*), 10.30 (br t, 1H, *J*=5.2 Hz, CSN*H*CH_2), 10.88 (br s, 1H, indole N*H*), 11.29 (s, 1H, N3*H*); δ_C 12.0, 23.0, 46.0, 55.9, 107.9, 111.2, 111.4, 118.3, 118.4, 121.0, 122.9, 127.1, 136.2, 142.6, 151.0, 164.6, 196.8; HRMS (FAB, dithioerythritol, dithiothreitol, glycerol): MH^+, found 343.1223. $C_{17}H_{19}N_4O_2S$ requires 343.1229.

***N*-[2-(4-Aminophenyl)ethyl](1-thyminyl)thioacetamide (3g).** 69%; mp 225–227°C; δ_H 1.77 (d, 3H, *J*=0.8 Hz, CH_3), 2.70 (t, 2H, *J*=7.4 Hz, CH_2CH_2C), 3.63 (dt, 2H, *J*=7.2, 5.9 Hz, CSNHCH_2), 4.56 (s, 2H, NCH_2CS), 4.91 (s, 2H, NH_2), 6.51 (d, 2H, *J* 8.2 Hz, benzene C*H*), 6.90 (d, 2H, *J*=8.2 Hz, benzene C*H*), 7.41 (d, 1H, *J*=1.1 Hz, C6*H*), 10.23 (br t, 1H, *J*=4.9 Hz, CSN*H*CH_2), 11.26 (br s, 1H, N3*H*); δ_C 11.9, 32.1, 47.2, 55.8, 107.9, 114.1, 125.7, 129.1, 142.7, 147.1, 151.1, 164.8, 197.0; HRMS (EI): M^+, found 318.1168. $C_{15}H_{18}N_4O_2S$ requires 318.1151. The hydrochloride salt of **3g** was crystallized from water, mp 234–235°C; δ_H 1.76 (d, 3H, *J*=0.9 Hz, CH_3), 2.91 (t, 2H, *J*=7.3 Hz, CH_2CH_2C), 3.74 (dt, 2H, *J*=7.1, 5.6 Hz, CSNHCH_2), 4.57 (s, 2H, NCH_2CS), 7.25 (d, 2H, *J*=8.5 Hz, benzene C*H*), 7.35 (d, 2H, *J*=8.5 Hz, benzene C*H*), 7.42 (d, 1H, *J*= 1.1 Hz, C6*H*), 9.94 (br s, 3H, NH_3^+), 10.35 (br t, 1H, *J*=5.1 Hz, CSN*H*CH_2), 11.28 (s, 1H, N3*H*).

Hydrolysis of *N*-[2-(4-imidazolyl)ethyl](1-thyminyl)-thioacetamide (3e)

The thioamide (**3e**, 100 mg, 0.34 mmol) in water (10 mL) was refluxed vigorously with stirring for 30 hours during which time hydrogen sulfide evolved. The hydrolysis mixture was evaporated to dryness. The residue was dissolved in hot methanol (ca. 60 mL), filtered, diluted with 2-propanol, and concentrated by distillation to a smaller volume. The crystals separated upon standing in the refrigerator, were collected by filtration and washed with 2-propanol to afford chromatographically pure amide **4e** (75 mg).

***N*-[2-(4-Imidazolyl)ethyl](1-thyminyl)acetamide (4e).** 79%; mp 249–251°C (dec.); δ_H 1.76 (d, 3H, *J*=0.8 Hz, CH_3), 2.65 (t, 2H, *J*=7.4 Hz, CH_2CH_2C), 3.30 (dt, 2H, *J*=7.4, 5.8 Hz, CONHCH_2), 4.27 (s, 2H, NCH_2CO), 6.85 (s, 1H, imidazole C5*H*), 7.44 (d, 1H, *J*=1.1 Hz, C6*H*), 7.62 (s, 1H, imidazole C2*H*), 8.25 (br t, 1H, *J*=5.4 Hz, CON*H*CH$_3$), 11.31 (br s, 1H, N3*H*); δ_C 11.9, 26.7, 38.9, 49.4, 108.0, 116.7, 134.2, 134.6, 142.4, 151.1, 164.6, 166.8; HRMS (EI): M^+, found 277.1179. $C_{12}H_{15}N_5O_3$ requires 277.1175.

Reactions of 1-(cyanobutyl)thymine (5) and 4-amidinobenzamide (7) with ammonium sulfide

1-(4-Amidinobutyl)thymine hydrochloride (6). The starting nitrile **5** (3.42 g, 0.0165 mol) was dissolved in pyridine (17 mL) and $(NH_4)_2S$, 20–22% solution in water (5.6 mL) was added. This solution was left to stand at ambient temperature over several months and examined by TLC with 7:5:2 $CHCl_3$–CH_3OH–NH_4OH as developing solvents. Removal of the solvents at room temperature gave an amidine. Solid free base was washed with cold water and changed into its white hydrochloride salt 6 (22%, not optimized) with 1N hydrochloric acid–tetrahydrofuran, mp 206°C; δ_H 1.60 (m, 4H, CH_2CH_2), 1.76 (s, 3H, CH_3), 2.42 (m, 2H, CH_2CNH_2), 3.66 (m, 2H, N1CH_2), 7.62 (d, 1H, *J*=1.1 Hz, C6*H*), 8.77 (s, 2H, *H*NC$^+$N*H*, restricted rotation[16]), 9.11 (s, 2H, *H*NC$^+$N*H*), 11.26 (s, 1H, N3*H*); δ_C 11.9, 23.2, 27.5, 31.2, 46.6, 108.5, 141.5, 150.9, 164.3, 170.8; HRMS (EI): M^+, found 224.1261. $C_{10}H_{16}N_4O_2$ requires 224.1273.

4-(Thiocarbamoyl)benzamide (8).[17] For the purpose of experimental verification of the mechanism, the mixture of amidine **7** (2.1578 g, 0.0108 mol) and ammonium sulfide, 20–22% solution in water (10 mL) was reacted and monitored by TLC (9:1 $CHCl_3$–CH_3OH) as above. The crude product was recrystallized from methanol to afford yellow crystals (75%); mp 224–225°C (dec.); δ_H 7.52 (s, 1H, CON*H*), 7.83–7.96 (m, 4H, C_6H_4), 8.10 (s, 1H, CON*H*), 9.63 (br s, 1H, CSN*H*), 10.01 (br s, 1H, CSN*H*); HRMS (EI): M^+, found 180.0371. $C_8H_8N_2OS$ requires 180.0357.

Syntheses directly from acetonitriles 9

N-[2-(3-Indolyl)ethyl](1-thyminyl)thioacetamide (**3f**) was obtained here by the second approach directly from (1-thyminyl)acetonitrile (**9b**, 2 g, 0.0121 mol) and tryptamine (**2f**, 1.9403 g, 0.0121 mol) in ethanol (30 mL) by refluxing for 18 hours with stirring in the presence of ammonium sulfide, 20–22% in water (5 mL). The crude product was washed with 2-propanol and worked up as described above for **3**. It was purified by repeated recrystallization from methanol to provide the desired product after standing for several days in the refrigerator (72%).

***N*-(2-Aminoethyl)(1-uracilyl)acetamide hydrochloride (10a).** One hour refluxing of (1-uracilyl)acetonitrile (**9a**, 2.1559 g, 0.0143 mol), ethylenediamine (0.8574 g, 0.0143 mol), ammonium sulfide, 20–22% solution in water (5.8 mL), in ethanol (40 mL) resulted in precipitation of the title compound. 2-Propanol (10 mL) was added and the reaction flask was kept in the refrigerator. The free base was collected by filtration and changed into its hydrochloride salt with 1N hydrochloric acid solution. After evaporation to dryness, the product was recrystallized from methanol to yield pure colourless material (74%), mp 224–225°C; ν_{max}(KBr) 3297, 3099, 1668, 1562, 1472, 1457, 1428, 1383, 1355, 1241, 1213, 1176 cm^{-1}; δ_H 2.85 (t, 2H, *J*=6.4 Hz, $CH_2CH_2NH_3^+$), 3.35 (dt, 2H, J 6.1, 5.9 Hz, NHCH_2CH$_2$), 4.38 (s, 2H, NCH_2CO), 5.57 (d, 1H,

J=7.8 Hz, C5*H*), 7.61 (d, 1H, J=7.8 Hz, C6*H*), 8.17 (br s, 3H, NH_3^+), 8.54 (br t, 1H, J=5.6 Hz, CON*H*CH_2), 11.24 (br s, 1H, N3*H*); δ_C 36.5, 38.4, 49.4, 100.6, 146.6, 151.1, 163.9, 167.6; HRMS (FAB, 3-nitrobenzyl alcohol): MH^+, found 213.1000. $C_8H_{13}N_4O_3$ requires 213.0988.

***N*-(2-Aminoethyl)(1-thyminyl)acetamide hydrochloride (10b).** This product was obtained by analogy to **10a** after overnight heating under reflux (78%), mp 238–239°C; ν_{max}(KBr) 3420, 3246, 3093, 2996, 1671, 1642, 1593, 1570, 1481, 1422, 1361, 1252, 1176 cm^{-1}; δ_H 1.75 (d, 3H, J=1.1 Hz, CH_3), 2.86 (t, 2H, J=6.4 Hz, $CH_2CH_2NH_3^+$), 3.35 (dt, 2H, J=6.1, 5.9 Hz, NHCH_2CH_2), 4.34 (s, 2H, NCH_2CO), 7.50 (d, 1H, J=1.2 Hz, C6*H*), 8.21 (br s, 3H, NH_3^+), 8.53 (br t, 1H, J=5.5 Hz, CON*H*CH_2), 11.31 (br s, 1H, N3*H*); δ_C 12.0, 36.5, 38.4, 49.3, 108.0, 142.3, 151.1, 164.5, 167.6; HRMS (FAB, 3-nitrobenzyl alcohol): MH^+, found 227.1129. $C_9H_{15}N_4O_3$ requires 227.1144. The salts **10** were fairly water-soluble solids. The spots were also detected by spraying the TLC plates with 0.2% ninhydrin ethanolic solution and heating (44:8:1 $CHCl_3$–CH_3OH–NH_4OH).

Synthesis of dicationic diaryl furan 12

2,5-Bis(4-cyanophenyl)furan (**11**, 1.7 g, 6.29 mmol), 1,3-diamino-2-hydroxypropane (5 g, 0.0555 mol), and ammonium sulfide, 20–22% in water (5 mL), were refluxed for 20 hours. The solid that sublimed during heating in the condenser was several times moved down using a glass spatula. After the reaction, water was added to a volume of 25 mL and the flask was kept overnight in the refrigerator. The precipitate was collected, successfully washed with cold water, and acidified with 1N HCl. Crystals were separated after addition of ethanol (91%). The material gave a positive ninhydrin test for primary amine (11:4:1 $CHCl_3$–CH_3OH–NH_4OH). On heating, the crystals decomposed, becoming brown, but did not melt below 300°C.

2,5-Bis{4-[*N*-(3-amino-2-hydroxypropyl)carbamoyl]-phenyl}furan dihydrochloride (12). ν_{max} (KBr) 3281, 3034, 2921, 1637, 1612, 1593, 1547, 1518, 1496, 1324, 1289, 1242, 1024 cm^{-1}; δ_H [D_2O, $(CH_3)_3SiCD_2CD_2CO_2Na$] 3.04 (dd, 2H, J=13.2, 9.9 Hz, C*H*NH_3^+), 3.27 (dd, 2H, J=13.2, 3.3 Hz, C*H*NH_3^+), 3.44 (dd, 2H, J=14.3, 6.9 Hz CONHC*H*), 3.51 (dd, 2H, J=14.3, 5.2 Hz, CONHC*H*), 4.15 (m, 2H, C*H*OH), 6.74 (s, 2H, furan C*H*), 7.50 (d, 4H, J=8.5 Hz, benzene C*H*), 7.63 (d, 4H, J=8.5 Hz, benzene C*H*); δ_H 2.71 (dd, 2H, J=12.9, 8.8 Hz, C*H*NH_3^+), 2.95 (dd, 2H, J=12.9, 2.7 Hz, C*H*NH_3^+), 3.25–3.50 (m, CONHCH_2, H_2O), 3.90 (m, 2H, C*H*OH), 5.74 (d, 2H, J=4.9 Hz, H-bonded O*H*), 7.30 (s, 2H, furan C*H*), 7.85–8.10 (m, 14H, C_6H_4, NH_3^+), 8.86 (t, 2H, J=5.6 Hz, CON*H*CH_2); δ_C 42.5, 43.2, 66.3, 110.0, 123.1, 127.9, 132.1, 132.6, 152.3, 165.8; HRMS (FAB, 3-nitrobenzyl alcohol): MH^+, found 453.2138. $C_{24}H_{29}N_4O_5$ requires 453.2138.

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