Heterocondensed Thiophenes and Thiazoles by THORPE-ZIEGLER Cyclization

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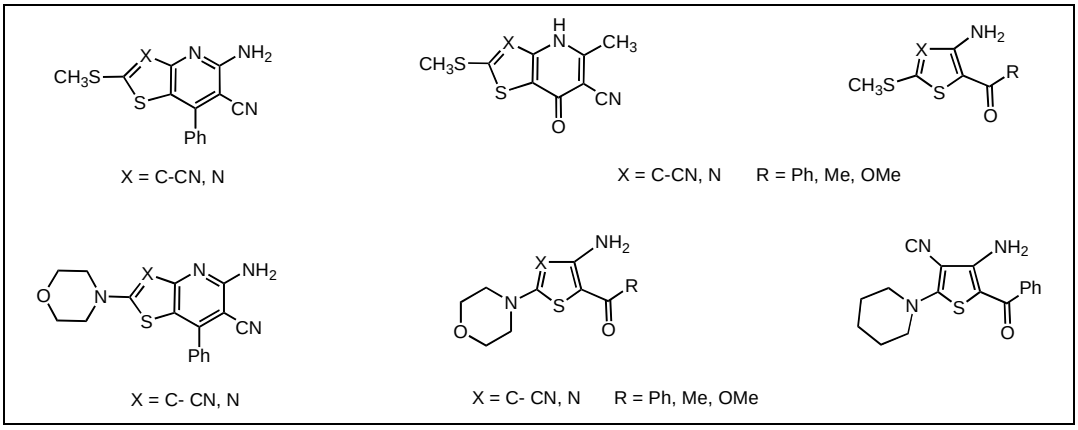

The syntheses of novel thieno-pyridones, thiazolo-pyridones, thiazolo-pyridines and amino- and diamino-dieno-pyridines were described. Simultaneously, it was demonstrated that in these compounds and in the related 3-aminothiophenes the replacement of the methylthio by the morpholino group is possible. The structures were characterized using ^{1}H-, ^{13}C-NMR, IR and elemental analysis.

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INTRODUCTION

In general the ZIEGLER-THORPE Cyclization [1] is designated as a intramolecular addition of a nitrile group on a activated methylene group, represented for example in Figure 1: with A, B = carbon or hetero atoms, X,Y = electron acceptors.

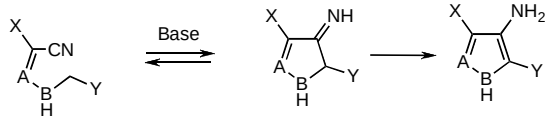


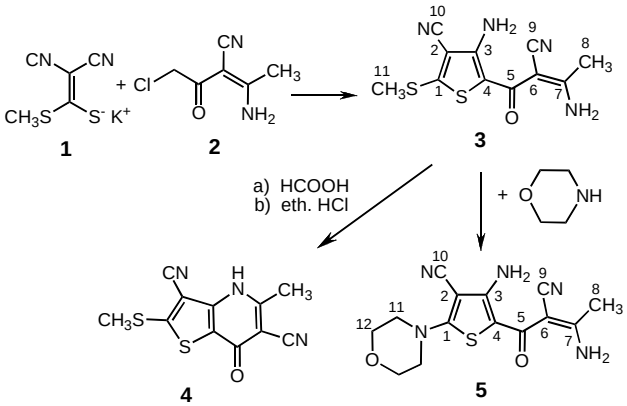
Figure 1

This reaction was used by us several times before for the preparation of amino-5-cycle-heterocycles [1], and herein cited literature, [2]. In the following we have tried to synthesize instantaneously condensed heterocycles by application of suitable reagents in one step or two steps.

RESULTS AND DISCUSSION

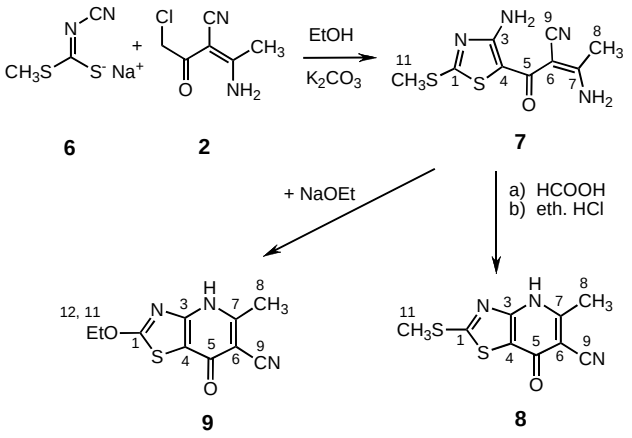
Mainly we are interested in the use of polyfunctional α-halogen compounds: Potassium-(2,2-dicyano-1-methyl-thioethen-1-yl)thiolate **1** [3,4] was reacted with 3-amino-2-chloracetyl-but-2-en-carbo-nitrile **2** [5] in boiling EtOH to give the thiophene derivative **3**, which formed the sparingly soluble thieno-pyridone **4** by acid catalysis. The structure was determined by ^{1}H NMR and mass spectrometry. Treatment of **3** with morpholine gives, *via* nucleophilic substitution of the methylthio group, the morpholino-thiophene **5** (see Scheme 1).

Scheme 1



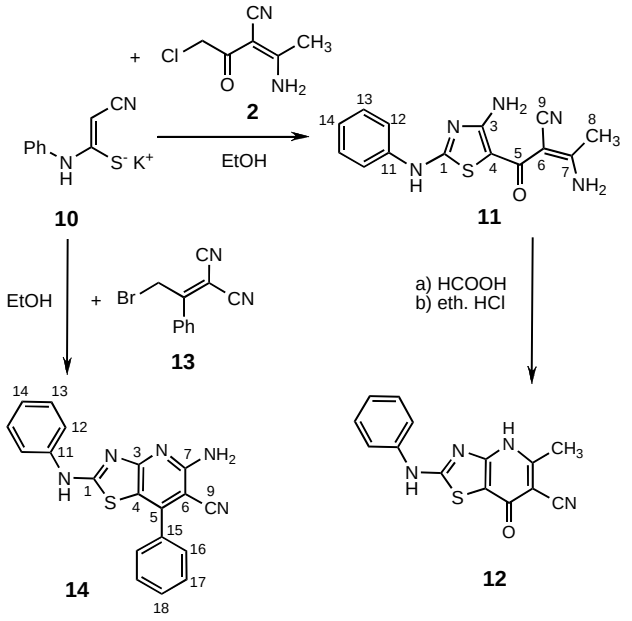
In the same manner, potassium-methyl-cyan-imido-dithiocarbonate **6** [6] reacted with **2** to form the 2-methylthiothiazole **7**. In presence of acid the reaction resulted in the thiazolo-pyridone **8**, whereas after treatment of **7** with NaOEt an nucleophilic substitution with formation of its ethoxy derivative **9** was observed (see Scheme 2).

Scheme 2



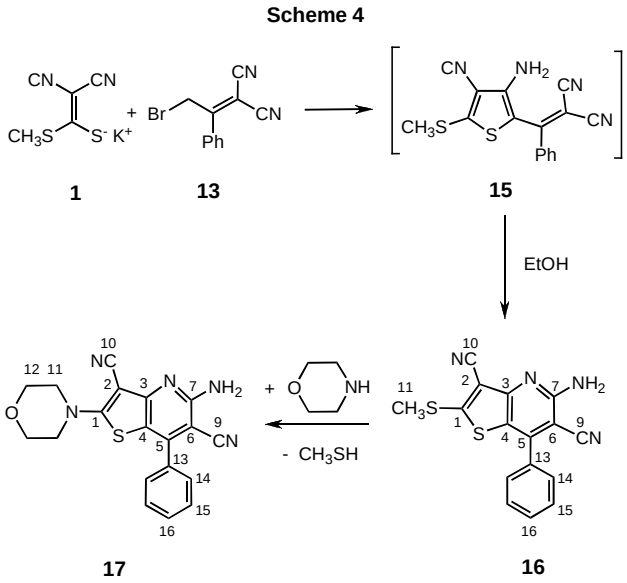
A further option was the reaction of sodium *N*-phenyl-*N*'-cyano-imido-thiocarbonate **10** [7] with **2** (see Scheme 3). After formation of the 4-amino-thiazole **11** the cyclization with acid to the thiazolo-pyridone **12** occured by elimination of ammonia. By reaction of 3-brommethyl-2-cyan-cinnamo-nitrile **13** [8] with **10** the diamino-thiazolo-pyridine **14** immediately was formed. Compound **13** (mp 118°C) was obtained from 2-cyan-3-methyl-cinnamo-nitrile [9] in boiling benzene with *N*-bromo-succinimide having been added.

Scheme 3



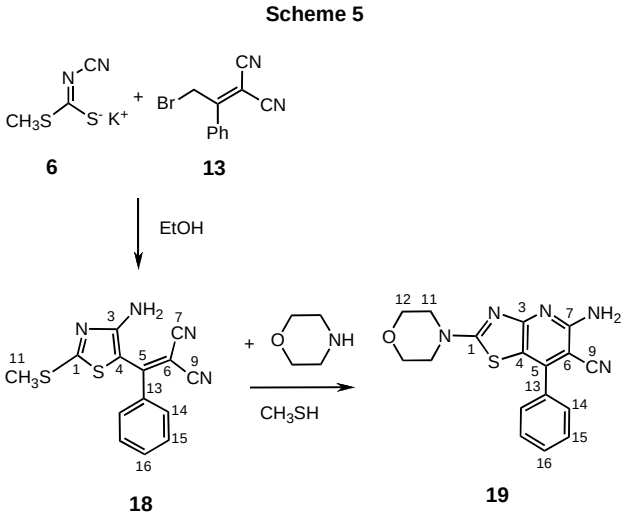
The direct cyclization to form the methylthio-thieno-pyridine **16** was achieved by the reaction of **1** with **13**. The intermediate 3-amino-thiophene derivative **15** could not be obtained. The nucleophilic substitution of CH_3S by the morpholino group lead to the thieno-pyridine **17** (see Scheme 4). To replace the methylthio group again compare thioglucolic ester [10].

Scheme 4



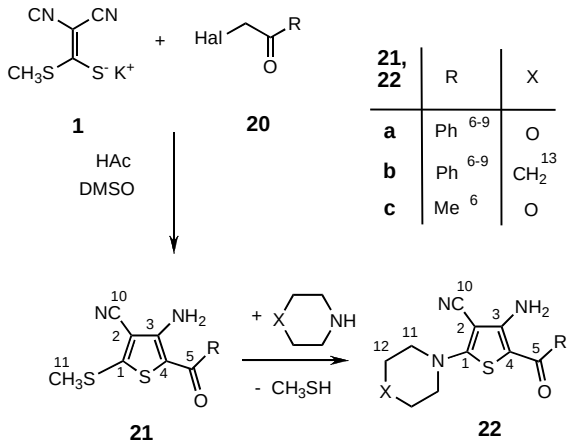
The replacement of malonitrile by cyanamide in the reaction of Potassium methylcyan-imido-dithiocarbonate **6** with the bromo-compound **13** yielded the substituted 4-amino-thiazole **18**. Beside the ring closure *via* the aminnitrile treatment with morpholine gave an nucleophilic substitution of the methylthio group at the thiazole ring, and the thiazolo-pyridine **19** was isolated (see Scheme 5).

Scheme 5



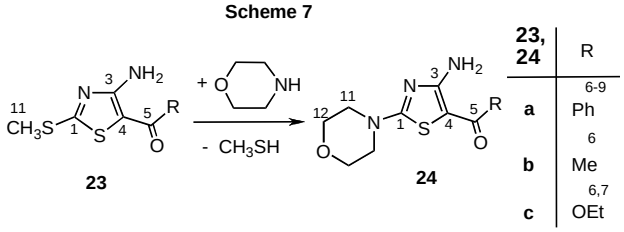
Furthermore the replacement of the CH_3S group by morpholine or piperidine could be applied to the THORPE products 4-amino-5-benzoyl-2-methylthio-thiophen-3-carbonitriles **21** and resulted in the morpholino-thiophenes **22** (see Scheme 6).

Scheme 6



In analogy to Wobig [11], the 4-amino-5-acyl-2-(4-morpholinyl)-thiazoles **24** were formed from the corresponding 2-methylthio-thiazoles **23** (Scheme 7).

Scheme 7



EXPERIMENTAL

The corrected melting points were measured on a Kofler hot-stage apparatus. ^{1}H and ^{13}C NMR spectra were obtained in DMSO-d_6 using the Bruker AC-300 and DRX-500 spectrometers. The ^{1}H and ^{13}C chemical shifts are reported in ppm downfield from TMS as an internal standard. Multiplicities in the: ^{13}C gated decoupling NMR spectra are given as a result of ^{13}C-^{1}H coupling over 2 or 3 bonds. The IR spectra were recorded on a spectrophotometer Specord 75 (Fa. Carl Zeiss Jena). Elemental analyses were determined on an EA 1108 (Fa. Carlo Erba Hofheim), the MS spectra by the HP Bruker Esquire LC-MS System.

Synthesis of compounds.

4-Amino-5-(3-amino-2-cyano-but-2-enoyl)-2-methylthio-thiophen-3-carbonitrile (**3**). 9.71g (0.05 mole) **1** and 7.85 g (0.05 mole) **2** was dissolved in 100 mL abs. ethanol and heated to reflux for 30 min. The reaction mixture was cooled and poured in 150 mL water. After short standing the product is isolated *in vacuo*. Yield: 7.9 g (57%), mp 245-250° (nitrometh. /acetic acid 1:1), ir: 3407, 3379,3297 (NH_2), 2214, 2194 (CN), 1620 (C=O), 1589 (C=C) cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 2.22 (s, 3H, CH_3), 2.70 (s, 3H, SCH_3), 7.55 (br. 2H, NH_2), 9.25, 10.52 (br., each 1H, NH_2), ^{13}C nmr (DMSO-d_6): δ 16.90 (C-11, SCH_3), 21.87 (C-8, CH_3), 77.12 (q, C-6), 97.72 (m, C-2), 104.87 (s, C-4), 112.73 (s, CN-10), 120.82 (s, CN-9), 156.07 (s, C-3), 157.34 (q, C-1), 172.06 (q, C-7), 180.60 (s, C-5, C=O). *Anal.* Calcd. for $C_{11}H_{10}N_4S_2$ (278.35) : C, 47.46; H, 3.62; N, 20.13; S, 23.04. Found: C, 47.26; H, 3.65; N, 19.94; S, 23.16.

2-Methyl-5-methylthio-4-oxo-1,4-dihydro-thieno[3,2-*b*]pyridin-3,6-dicarbonitrile (4).

a) 1.35 g (0.005 mol) **3** and 10 mL formic acid were heated to reflux for 2 h. After cooling the solution was diluted with 50 mL water and the filtrate was evaporated. Yield: 1.19 g (91%), mp >360° (DMF/H_2O 1:1), ir: 3428 (NH), 2242, 2211 (CN), 1608 (C=O), 1495 (C=C), 1392 (CH_3) cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 2.47 (s, 3H, CH_3), 2.77 (s, 3H, SCH_3), 12.5 (br., 1H, NH), ms: m/z 261 (100%) [M$^+$], *Anal.* Calcd. for $C_{11}H_7N_3OS_2$ (261.32) : C, 50.56; H, 2.70; N, 16.08; S, 24.54. Found: C, 50.20, H, 2.69; N, 15.89; S, 24.20.

b) 0.97 g (0.004 mole) **3** dissolved in 15 mL abs. ethanol was heated with 5 mL conc. Hydrochloric acid to reflux for 10 min. After cooling the white precipitate was collected by filtration; Yield: 0.24 g (23%), mp >360° (DMF/H_2O 1:1). *Anal.* Found: C, 50.21; H, 2.62; N, 15.95; S, 24.20.

2-Methyl-5-morpholino-4-oxo-1,4-dihydro-thieno[3,2-*b*]-pyridin-3,6-dicarbonitrile (5). A solution of 2.76 g (0.01 mol) **3** in 10 mL morpholine was heated to reflux for 1 h. After evaporation of the morpholine, the residual product was poured in water and purified by filtration. Yield: 0.75 g (24%), mp >360° (ethanol/water 1:1), ir: 3420, (NH_2), 2900, 2800 (CH_2), 2204 (CN), 1615 (C=O), 1557, 1497 (C=C) 1125 (CH_2) cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 3.43, 3.56 (t, each 4H, CH_2), 9.29, 9.68 (br., each 1H, NH_2), ^{13}C nmr (DMSO-d_6): δ 23.70 (C-8, CH_3), 47.81. (C-11, NCH_2), 65.66 (C-12, OCH_2), 92.97 (s, C-4), 113.32 (s, CN-10), 120.33 (s, CN-9), 152.61 (s, C-3), 157.87 (m, C-1), 170.05 (q, C-7), 178.32 (s, C-5, C=O). *Anal.* Calcd. for $C_{14}H_{15}N_5O_2S$ (317.37) : C, 52.98; H, 4.76; N, 22.07; S, 10.10. Found: C, 52.69; H, 4.71; N, 21.94; S, 10.40.

4-Amino-5-(3-amino-2-cyano-but-2-enoyl)-2-methylthio-thiazole (7). 3.40 g (0.02 mole) **6** and 3.16 g (0.02 mole) **2** were heated with 7 g (0.05 mole) anhydrous potassium carbonate and 50 mL abs. ethanol to reflux for 2 h. After cooling the reaction mixture was diluted with 100 mL water and the residual filtrate was purified in the evaporator. Yield: 0.17 g (33%), mp >199-202° (CH_3CN), ir: 3390, 3314, 3143 (NH_2), 2191 (CN), 1628 (C=O), 1608, 1577 (C=C), 1385 (CH_3) cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 2.65 (s, 3H, SCH_3), 7.71 (br, 2H, NH_2), 8.95, 10.55 (br., each 1H, NH_2), ^{13}C nmr (DMSO-d_6): δ 15.30 (C-11, SCH_3), 21.75 (C-8, CH_3),. 77.69 (m, C-6), 97.55 (t, C-4), 121.21 (s, CN-9), 165.20 (s, C-3) 171.24 (m, C-7), 171.58 (q, C-1), 180.27 (s, C-5, C=O). *Anal.* Calcd. for $C_9H_{10}N_4OS_2$ (254.32) : C, 42.50; H, 3.96; N, 22.03; S, 25.21. Found: C, 42.45; H, 3.96; N, 22.11; S, 25.20.

2-Methyl-6-methylthio-4-oxo-1,4-dihydro-thiazolo[5,4-*b*]pyridin-3-carbonitrile (8).

a) 0.26 g (0.001 mole) **7** was heated in 5 mL formic acid to reflux for 2h. After cooling the product was concentrated by evaporation and washed with sodium hydrogen carbonate and water. Yield: 0.21 g (88%), mp >360° (DMF/H_2O 1:1), ir: 3443(NH), 2966, 2903(CH_3), 2228 (CN), 1618(C=O) cm^{-1}, ^{1}H nmr (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 13.6 (br, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 16.19 (C-11, SCH_3), 18.65 (C-8, CH_3),. 96.80 (q, C-6), 115.93 (s, CN-9), 118.54 (s, C-4), 153.22 (s, C-3), 155.37 (q, C-7), 169.22 (q, C-1), 176.08 (s, C-5, C=O). ms m/z 237 (100%) [M$^+$], *Anal.* Calcd. for $C_9H_7N_3OS_2$

(237.29): C, 45.55; H, 2.97; N, 17.71; S, 27.02. Found: C, 45.71; H, 2.96; N, 17.78; S, 27.19.

b) 1.25 g (0.005 mole) **7** in 15 mL ethanol was heated to reflux with 5 mL conc. hydrochloric acid for 2h. The mixture was cooled, purificated in the evaporator and washed with sodium hydrogencarbonate and water. Yield: 0.97 g (82%), mp >360° (DMF/H_2O 1:1), *Anal.* Found: C, 45.29; H, 2.91; N, 17.66; S, 27.12.

2-Methyl-6-ethoxy-4-oxo-1,4-dihydro-thiazolo[5,4-*b*]pyridin-3-carbonitrile (9). 1.25 g (0.05 mole) sodium was dissolved in 50 mL abs. ethanol and heated with 0.76 g (0.003 mole) **7** to reflux 15 min. The mixture was cooled and poured in 100 mL ice water acidificated with hydrochloric acid. The precipitate was collected after evaporation of solvents. Yield: 0.26 g (37%), mp >279-282° (*n*-propanol), ir: 3440 (NH), 2926, 2854 (CH_3, CH_2), 2214 (CN), 1611 (C=O) 1589, 1553, 1519 (C=C), 1255 (OCH_2) cm^{-1}, ^1H nmr (DMSO-d_6): δ 1.45 (t, 3H, CH_3), 2.50 (s, 3H, CH_3), 4.55 (q, 2H, OCH_2), 13.7 (br, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 14.01 (C-12, CH_3), 18.54 (C-8, CH_3), 59.86 (C-11, OCH_2), 97.13 (m, C-6), 113.10 (s, C-4), 115.89 (s, CN-9), 149.87 (q, C-7), 154.20 (s, C-3), 169.51 (t, C-1), 177.25 (s, C-5, C=O). *Anal.* Calcd. for $C_{10}H_9N_3O_2S$ (235.26) : C, 51.05; H, 3.86; N, 17.86; S, 13.63. Found: C, 50.91; H, 3.91; N, 17.76; S, 13.76.

4-Amino-2-anilino-5-(3-amino-2-cyano-but-2-enoyl)-thiazole (11). During the stirring 2.03 g (0.01 mole) **10** and 1.58 g (0.01 mole) **2** were dissolved in 25 mL abs. ethanol and heated in a boiling water bath for 25 min. After cooling the mixture was diluted with 50 mL water und purificated by filtration. Yield: 1.8 g (60%), mp >237-239° (CH_3NO_2), ir: 3450, 3300 (NH_2,NH), 3150, 3100 (CH_{ar}), 2186 (CN), 1610 (C=O) 1440, 1371 (CH_3) cm^{-1}, ^1H nmr (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 7.01 (t, 1H , *p*-CH), 7.32 (t, 2H, *m*-CH), 7.65 (d, 2H, *o*-CH), 7.85 (br, 2H, NH_2), 8.62, 1054 (br., each 1H, NH_2), 10.6 (br, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 21.70 (C-8, CH_3), 77.33 (m, C-6), 89.45 (t, C-4), 118.51 (t, *o*-C-12), 121.68 (s, CN-9), 122.71 (t, *p*-C-14), 128.97 (d, *m*-C-13), 140.03 (t, *i*-C-11), , 165.17 (s, C-1), 165.41 (s, C-3), 170.24 (q, C-7), 179.86 (s, C-5, C=O). *Anal.* Calcd. for $C_{14}H_{13}N_5OS$ (299.35) : C, 56.17; H, 4.38; N, 23.40; S, 10.71. Found: C, 56.14; H, 4.40; N, 23.52; S, 10.62.

6-Anilino-2-methyl-4-oxo-1,4-dihydro-thiazolo[5,4-*b*]pyridin-3-carbonitrile (12).

a) 0.30 g (0.001 mole) **11** dissolved in 5 mL formic acid was heated to reflux for 2 h. After cooling the product was collected in an evaporator and washed with sodium hydrogencarbonate and water. Yield: 0.2 g (71%), mp >360° (DMF/H_2O 1:1), ir: 3300 (NH), 3150, 3100 (CH_{ar}), 2221 (CN), 1607 (C=O), 1555 (C=C), 1460 (CH_3), 750, 650 (C_{ar}) cm^{-1}, ms: m/z 282 (25%)[M^+], 222 (75%), *Anal.* Calcd. for $C_{14}H_{10}N_4OS$ (282.32): C, 59.36; H, 3.57; N, 19.85; S, 11.36. Found: C, 59.24; H, 3.60; N, 19.47; S, 11.52.

b) 0.30 g (0.001 mole) **11** in 15 mL abs. ethanol was heated with 5 mL conc. hydrochloric acid to reflux 2 h. After cooling the mixture was diluted with 20 mL water, purified in the evaporator and washed with a solution of sodium hydrogen carbonate and water. Yield: 0.25 g (88%), mp >360° (DMF/H_2O 1:1). *Anal.* Found: C, 59.14; H, 3.69; N, 19.55; S, 11.02.

2-Amino-5-anilino-4-phenyl-thiazolo[5,4-*b*]pyridin-3-carbonitrile (14). 2.03 g (0.01 mole) **10** and 2.47 g (0.01 mole) **13** in 25 mL abs. ethanol was heated to reflux for 2h. The mixture was cooled and poured in 30 mL water and purified *in vacuo*. Yield: 3.0 g (88%), mp >310-312° (*n*-propanol/ac.acid 1:1), ir: 3427, 3300 (NH_2,NH), 3150 (CH_{ar}), 2204, (CN), 1614 (NH_2) 1542, 1454 (C=C), 750, 700 (C_{ar}) cm^{-1}, ^1H nmr (DMSO-d_6): δ 6.80 (br, 2H, NH_2), 7.05-7.80 (m, 10H , CH_{ar}), 10.97 (br, 1H, NH). ^{13}C nmr (DMSO-d_6): δ 83.03 (t, C-6), 111.92 (s, C-4), 117.53 (t, *o*-C-11), 117.28 (s, CN-9), 124.53 (t, *p*-C-14), 128.57 (d, *m*-C-13), 129.41 (t, *o*-C-16), 129.60 (d, *m*-C-17), 131.54 (t, *p*-C-18), 135.82 (t, *i*-C-15), 141.22 (t, *i*-C-11), 146.72 (t, C-5), 160.68 (s, C-7), 165.44 (s, C-3), 167.43 (s, C-1). *Anal.* Calcd. for $C_{19}H_{13}N_5S$ (343.41) : C, 62.42; H, 3.82; N, 20.39; S, 9.34. Found: C, 62.80; H, 3.83; N, 20.68; S, 9.24.

5-Amino-2-methylthio-7-phenyl-thieno[3,2-*b*]pyridin-3,6-dicarbonitrile (16). 3.88 g (0.02 mole) **1** and 4.95 g (0.02 mole) **13** were mixed in 80 mL ethanol, stirred and heated to reflux for 2 h. After cooling the reaction mixture was diluted with 80 mL water. The yellow precipitate was washed with ethanol and collected by filtration. Yield: 2.75 g (42%), mp >295-297° (CH_3NO_2), ir: 3473, 3328, 3220 (NH_2), 3120 (CH_{ar}), 2215, 2205 (CN), 1623, 1513 (C=C), 770, 700 (C_{ar}) cm^{-1}, ^1H nmr (DMSO-d_6): δ 2.75 (s, 3H, SCH_3), 7.28 (br, 2H, NH_2), 7.6-7.7 (m, 5H, CH_{ar}); ^{13}C nmr (DMSO-d_6): δ 16.39 (C-11, SCH_3), 87.73 (t, C-6), 101.11 (q, C-2), 113.02 (s, C-4), 118.28 (s, CN-9), 129.47 (t, *o*-C-14), 129.50 (d, *m*-C-15), 131.47 (t, *p*-C-16), 135.66 (t, *i*-C-13), 148.82 (t, C-5), 155.94 (s, C-3) 159.88 (s, C-7), 165.23 (s, C-1). *Anal.* Calcd. for $C_{16}H_{10}N_4S_2$ (322.42) : C, 59.60; H, 3.13; N, 17.38; S, 19.89. Found: C, 59.64; H, 3.14; N, 17.48; S, 19.74.

5-Amino-2-(4-morpholinyl)-7-phenyl-thieno[3,2-*b*]pyridin-3,6- dicarbonitrile (17). 0.64 g (0.002 mole) **16** was heated with 5 mL morpholine to reflux for 30 min. The product was collected after evaporation. Yield: 0.65 g (90%), mp >365°, decomp. (DMF/H_2O), ir: 3416, 3350, 3210 (NH_2), 2950, 2900, 2850 (CH_2), 2203 (CN), 1646, 1523 (C=C), 1417 (CH_2), 760, 700 (C_{ar}) cm^{-1}, ^1H nmr (DMSO-d_6): δ 3.6-3.8 (br, 8H, NCH_2,CH_2O), 6.95 (br, 2H, NH_2), 7.5-7.7 (m, 5H, CH_{ar}),. ^{13}C nmr (DMSO-d_6): δ 46.39 (C-11, NCH_2), 66.89 (C-12, OCH_2), 79.64 (s, C-2), 84.23 (t, C-6), 110.02 (s, C-4), 115.88 (s, CN-9), 129.11 (t, *o*-C-14), 129.78 (d, *m*-C-15), 131.03 (t, *p*-C-16), 134.83 (t, *i*-C-13), 147.12 (t, C-5), 158.34 (s, C-3) 160.13 (s, C-7), 168.83 (m, C-1). *Anal.* Calcd. for $C_{19}H_{15}N_5OS$ (361.42) : C, 63.14; H, 4.18; N, 19.38; S, 8.87. Found: C, 62.98; H, 4.17; N, 19.44; S, 8.82.

3-(4-Amino-2-methylthiothiazolyl)-3-cyan-cinnamalidennitrile (18). 1.70 g (0.01 mole) **6** and 2.45 g (0.01 mole) **13** dissolved in 50 mL abs. ethanol, were heated to reflux for 90 min. After standing over night 100 mL water was added, the mixture was filtered and washed with water. Yield: 1.12 g (38%), mp 219-221° (ethanol), ir: 3440, 3325 (NH_2), 2214 (CN), 1623 (C=C), 1439, 1389 (CH_3), 750, 700 (C_{ar}) cm^{-1}, ^1H nmr (DMSO-d_6): δ 2.69 (s, 3H, SCH_3), 7.15 (br, 2H, NH_2), 7.5-7.7 (m, 5H, CH_{ar}),. ^{13}C nmr (DMSO-d_6): δ 15.65 (C-11, SCH_3), 67.83 (t, C-6), 100.39 (t, C-4), 115.87 (s, CN-7), 116.30 (s, CN-9), 129.33 (t, *o*-C-14), 129.43 (d, *m*-C-15), 131.47 (t, *p*-C-16), 135.82 (t, *i*-C-13), 161.35 (t, C-5), 162.88 (s, C-3), 178.21 (q, C-1). *Anal.* Calcd. for $C_{14}H_{10}N_4OS_2$ (298.38) : C, 56.36; H, 3.38; N, 18.87; S, 21.49. Found: C, 56.16; H, 3.35; N, 18.68; S, 21.40.

2-Amino-4-phenyl-6-(4-morpholinyl)-thiazolo[5,4-*b*]pyridin-3-carbonitrile (19). 0.89 g (0.003 mole) **18** was heated with 5 mL morpholine to reflux for 30 min. The morpholine was evaporated and the residue poured in water and was purified. Yield: 0.71 g (70%), white-yellow crystals, mp 273-274, (*n*-propanol), ir: 3415 (NH_2), 2950, 2900, 2850 (CH_2), 2198 (CN), 1522, (C=C), 1419 (CH_2), 770, 700 (C_{ar}) cm^{-1}, ^1H nmr (DMSO-

d$_6$): δ 3.55 -3.75 (br, 8H, NCH_2,CH_2O), 6.71 (br, 2H, NH_2), 7.55 (m, 5H, CH_{ar}),. ^{13}C nmr (DMSO-*d*$_6$): δ 47.43 (C-11, NCH_2), 68.09 (C-12, OCH_2), 81.93 (t, C-6), 112.32 (s, C-4), 117.28 (s, CN-9), 129.23 (t, *o*-C-14), 129.38 (d, *m*-C-15), 131.26 (t, *p*-C-16), 135.03 (t, *i*-C-13), 146.32 (t, C-5), 165.74 (s, C-3) 160.71 (s, C-7), 172.43 (m, C-1). *Anal.* Calcd. for $C_{17}H_{15}N_5OS$ (337.40): C, 60.52; H, 4.48; N, 20.76; S, 9.50. Found: C, 60.53; H, 4.53; N, 20.81; S, 9.38.

4-Amino-5-benzoyl-2-methylthio-thiophen-3-carbonitrile (21a). 1.94 g (0.01 mole) **1** dissolved in 15 mL DMSO was dropped under stirring at 60°C to 1.99 g (0.01 mole) phenacyl bromide dissolved in 3 mL glacial acetic acid. After stirring for 30 min the mixture was poured in 50 mL water and after 1-2 h the precipitate was collected by filtration and crystallized in ethanol. Furthermore the product can be washed with CS_2. Yield: 1.73 g (63%), mp 149-151° (ethanol), ir: 3400, 3312, 3288 (NH_2), 2220 (CN), 1594 (C=O), cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 2.65 (s, 3H, SCH_3), 7.45-7.70 (m, 5H , CH_{ar}) 7.90 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$): δ 16.66 (C-11, SCH_3), 96.99 (t, C-2), 106.21 (t, C-4), 112.36 (s, CN-10), 127.07 (t, *o*-C-7), 128.57 (d, *m*-C-8), 131.23 (t, *p*-C-9), 140.05 (t, *i*-C-6), 156.45 (s, C-3), 162.39 (q, C-1), 185.40 (t, C-5, C=O). *Anal.* Calcd. for $C_{13}H_{10}N_2OS_2$ (274.36) : C, 56.91; H, 3.67; N, 10.21; S, 23.37. Found: C, 56.93; H, 3.70; N, 10.19; S, 23.44.

4-Amino-5-benzoyl-2-(4-morpholinyl)-thiophen-3-carbonitrile (22a). 4.12 g (0.015 mole) **21a** was heated with 35 mL morpholine to reflux for 45 min. After cooling the product was poured in 350 mL water and the yellow crystals were collected by filtration. Yield: 2.78 g (61%), mp 240-241° (CH_3CN), ir: 3407, 3338 (NH_2), 3150, (CH_{ar}). 2950, 2900 (CH_2), 2200, 2198 (CN), 1607 (C=O), 1557 (C=C), 1474, 1113 (CH_2), 750, 700 (C_{ar}) cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 3.60, 3.75 (t, each 4H, NCH_2CH_2O), 7.40-7.70 (m, 5H , CH_{ar}) 7.91 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$): δ 50.02 (C-11, NCH_2), 65.74 (C-12, OCH_2), 79.02 (t, C-2), 95.81 (t, C-4), 115.13 (s, CN-10), 127.22 (t, *o*-C-7), 128.40 (d, *m*-C-8), 130.80 (t, *p*-C-9),), 140.75 (t, *i*-C-6), 157.79 (s, C-3), 167.66 (q, C-1), 185.92 (t, C-5, C=O). *Anal.* Calcd. for $C_{16}H_{15}N_3O_2S$ (313.37) : C, 61.13; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.23; H, 4.75; N, 13.61; S, 10.34.

4-Amino-5-benzoyl-2-(1-piperidinyl)-thiophen-3-carbonitrile (22b). 2.28 g (0.008 mole) **21a** was dissolved in 20 mL piperidine and heated to reflux for 30 min. After cooling the mixture was poured in 200 mL water and concentrated by evaporation. Yield: 1.48 g (59%), mp 161° (CH_3CN), ir: 3395 (NH_2),. 2900, 2850 (CH_2), 2199 (CN), 1599 (C=O), 1549, 1482, 1461 (C=C), 730, 700 (C_{ar}) cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 1.5 (s, 6H, CH_2), 3.50, (m, 4H, NCH_2), 7.40-7.70 (m, 5H , CH_{ar}) 7.95 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$): δ 22.87 (C-13, CH_2), 24.86 (C-12, CH_2), 51.45 (C-11, NCH_2), 76.31 (t, C-2), 93.18 (t, C-4), 115.31 (s, CN-10), 126.77 (t, *o*-C-7), 128.42 (d, *m*-C-8), 130.42 (t, *p*-C-9),), 140.98 (t, *i*-C-6), 159.22 (s, C-3), 166.67 (q, C-1), 183.77 (t, C-5, C=O). *Anal.* Calcd. for $C_{16}H_{15}N_3O_2S$ (301.40) : C, 65.57; H, 5.50; N, 13.49; S, 10.30. Found: C, 65.63; H, 5.55; N, 13.61; S, 10.34.

5-Acetyl-4-amino-2-methylthio-thiophen-3-carbonitrile (21c). To a stirred solution of 5.83 g (0.03 mole) **1** in 60 mL DMSO was dropped over 15 min 2.78 g (0.031 mole) chloroacetone. After further stirring for 30 min at 60°C the reaction mixture was poured in 200 mL water and the precipitate was collected after evaporation. Yield: 1.20 g (18%), mp 205-207° (CH_3NO_2), ir: 3366 (NH_2), 2207 (CN), 1604 (C=O), 1505 (C=C), 1405, 1380 (CH_3), cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 2.22 (s, 3H, CH_3), 2.69 (s, 3H, SCH_3), 7.50 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$): δ 16.85 (C-11, SCH_3), 28.17 (C-6, CH_3), 97.32 (t, C-2), 107.91 (t, C-4), 112.96 (s, CN-10), 154.18 (s, C-3), 159.81 (q, C-1), 187.92 (q, C-5, C=O). *Anal.* Calcd. for $C_8H_8N_2OS_2$ (212.28) : C, 45.23; H, 3.80; N, 13.20; S, 30.21. Found: C, 45.19; H, 3.84; N, 13.22; S, 30.56.

5-Acetyl-4-amino-2-(4-morpholinyl)-thiophen-3-carbonitrile (22c). 1.27 g (0.006 mole) **21c** was heated with 5 mL morpholine to reflux for 30 min. The surplus morpholine was evaporated and the residue poured in ice-cold saturated solution of NaCl in water was purified by filtration. Yield: 0.67 g (45%), green crystals, mp 275-277° (CH_3NO_2/CH_3CN 1:1), ir: 3413, 3383 (NH_2), 2950, 2900, 2850 (CH_2), 2201 (CN), 1600 (C=O), 1501 (C=C), 1245, 1116 (CH_2), cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 2.22 (s, 3H, CH_3), 3.62, 3.75 (t, each 4H, NCH_2CH_2O), 7.51 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$): δ 27.80 (C-6, CH_3), 49.76 (C-11, NCH_2), 65.04 (C-12, OCH_2), 79.33 (t, C-2), 104.81 (t, C-4), 115.08 (s, CN-10), 162.10 (s, C-3), 166.20 (m, C-1), 183.52 (q, C-5, C=O). *Anal.* Calcd. for $C_{11}H_{13}N_3O_2S$ (251.31) : C, 52.57; H, 5.21; N, 16.72; S, 12.75. Found: C, 52.48; H, 5.17; N, 16.60; S, 12.38.

4-Amino-5-benzoyl-2-methylthio-thiazole (23a). To a solution of 3.40 g (0.02 mole) **6** in 30 mL ethanol was dropped a solution of 3.98 g (0.02 mole) phenacyl bromide in 10 mL ethanol. The mixture was heated to reflux for 10 min and after cooling the product was taken and purified by an evaporator. Yield: 3.96 g (81%), mp 149-151° (ethanol), ir: 3374, 3275 (NH_2), 1598 (C=O), 1470, 1376 (CH_3), 737, 695 (C_{ar}) cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 2.66 (s, 3H, SCH_3), 7.46-7.71 (m, 5H, CH_{ar}) 8.10 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$) (in accordance with [11]): δ 15.46 (C-11, SCH_3), 99.95 (t, C-4), 126.87 (t, *o*-C-7), 128.55 (d, *m*-C-8), 131.07 (t, *p*-C-9), 141.07 (t, *i*-C-6), 165.12 (s, C-3), 175.58 (q, C-1), 184.25 (t, C-5, C=O). *Anal.* Calcd. for $C_{11}H_{10}N_2OS_2$ (250.33) : C, 52.78; H, 4.03; N, 11.19; S, 25.67. Found: C, 52.78; H, 4.03; N, 11.12; S, 25.35.

4-Amino-5-benzoyl-2-(4-morpholinyl)-thiazole (24a). 0.37 g (0.0015 mole) **23a** was heated with 5 mL morpholine to reflux for 30 min. The morpholine was evaporated and the residue was poured in 50 mL water and purificated by filtration. Yield: 0.34 g (78%), mp 182-184° (*n*-propanol), ir: 3375, 3250 (NH_2), 2950, 2900, 2850 (CH_2), 1603 (C=O), 1540 (C=C), 1486, 1468, 1431 (CH_2), 737, 702 (C_{ar}) cm^{-1}. ^{13}C nmr (DMSO-*d*$_6$) (in accordance with [12]): δ 47.46 (C-11, NCH_2), 65.27 (C-12, OCH_2), 93.02 (t, C-4), 126.63 (t, *o*-C-7), 128.30 (d, *m*-C-8), 130.16 (t, *p*-C-9), 141.90 (t, *i*-C-6), 166.08 (s, C-3), 171.81 (m, C-1), 182.19 (t, C-5, C=O). *Anal.* Calcd. for $C_{14}H_{15}N_3O_2S$ (289.35) : C, 58.11; H, 5.23; N, 14.52; S, 11.08. Found: C, 58.23; H, 5.25; N, 14.54; S, 11.02.

4-Amino-5-acetyl-2-methylthio-thiazole (23b). To a slowly stirred solution of 8.52 g (0.05 mole) **6** in 50 mL ethanol was dropped 4.63 g (4 mL, 0.05 mole) chloroacetone dissolved in 25 mL ethanol. After heating for 15 min to reflux 1 mL trietylamine was added. The residue was poured in 50 mL water and the precipitate was collected after filtration. Yield: 1.89 g (10%), mp 155-156° (ethanol), ir: 3396, 3290 (NH_2), 1616 (C=O), 1487 (C=C), 1388 (CH_3), cm^{-1}, ^{1}H nmr (DMSO-*d*$_6$): δ 2.21 (s, 3H, CH_3), 2.67 (s, 3H, SCH_3), 7.62 (br, 2H, NH_2). ^{13}C nmr (DMSO-*d*$_6$) (in accordance with [11]): δ 15.54 (C-11, SCH_3), 29.24 (C-6, CH_3), 101.75 (m, C-4), 162.75 (s, C-3), 172.78 (q, C-1), 186.95 (q, C-5, C=O). Anal. Calcd. for $C_6H_8N_2OS_2$ (188.26) : C, 38.28; H, 4.28; N, 14.88; S, 43.06. Found: C, 38.24; H, 4.28; N, 14.89; S, 34.01.

4-Amino-5-acetyl-2-(4-morpholinyl)-thiazole (24b). 1.0 g (0.053 mole) **23b** was heated with 5 mL morpholine to reflux for 30 min. The morpholine was evaporated and the residue was poured in 50 mL water and purificated by filtration. Yield: 0.83 g (70%), mp 169-170° (ethanol), ir: 3375, 3272, 3166 (NH_2), 2950, 2900 (CH_2), 1612 (C=O), 1529 (C=C), 1466 (CH_2), 1375 (CH_3) cm^{-1}. ^1H nmr (DMSO-d_6): δ 2.06 (s, 3H, CH_3), 3.46, 3.68 (t, each 4H, NCH_2CH_2O), 7.64 (br, 2H, NH_2). ^{13}C nmr (DMSO-d_6): δ 28.68 (C-6, CH_3), 47.42 (C-11, NCH_2), 65.29 (C-12, OCH_2), 96.41 (t, C-4), 163.71 (s, C-3), 170.31 (m, C-1), 184.64 (q, C-5, C=O). *Anal.* Calcd. for $C_9H_{13}N_3O_2S$ (227.32) : C, 47.56; H, 5.77; N, 18.49; S, 14.11. Found: C, 47.57; H, 5.83; N, 18.52; S, 14.10.

4-Amino-2-methylthio-thiazole-5-carboxylic-ethylester (23c). To a slowly stirred solution of 8.52 g (0.05 mole) **6** in 50 mL ethanol was dropped 6.13 g (5.3 mL, 0.05 mole) chloro-acetic acid ethyl ester dissolved in 25 mL ethanol. After heating for 15 min to reflux 1mL trietylamine was added and the mixture was heated to reflux for 2 h. The solvent was evaporated *in vacuo* and the residue poured in 50 mL water was collected by filtration. Yield: 3.31 g (30%), mp 100-102° (ethanol), ir: 3445, 3300 (NH_2), 1664 (C=O), 1613 (C=C), 1378 (CH_3), 1301, 1096 (CH_2) cm^{-1}. ^1H nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_3), 2.66 (s, 3H, SCH_3), 4.18 (q, 2H, OCH_2), 7.02 (br, 2H, NH_2). ^{13}C nmr (DMSO-d_6): δ 14.42 (C-7, CH_3), 15.52 (C-11, SCH_3), 59.68 (C-6, OCH_2), 89.47 (t, C-4), 162.59 (t, C-5, C=O), 163.12 (s, C-3), 172.41 (q, C-1). *Anal.* Calcd. for $C_7H_{10}N_2O_2S_2$ (218.29) : C, 38.52; H, 4.62; N, 12.83; S, 29.37. Found: C, 38.64; H, 4.66; N, 12.75; S, 29.41.

4-Amino-2-(4-morpholinyl)-thiazole-5-carboxylic-ethylester (24c). 1.09 g (0.005 mole) **23c** was heated with 5 mL morpholine to reflux for 7 h. The morpholine was evaporated, the residue was poured in 50 mL water and the white crystals were collected by filtration. Yield: 0.68 g (53%), mp 130-133° (*n*-propanol), ir: 3420, 3317 (NH_2), 2950, 2900 2850 (CH_2), 1661 (C=O), 1628 (NH_2), 1539, 1518 (C=C), 1429, 1368, 1117 (CH_3, CH_2) cm^{-1}. ^{13}C nmr (DMSO-d_6): δ 14.59 (C-7, CH_3), 47.26 (C-11, NCH_2), 58.73 (C-6, OCH_2), 65.27 (C-12, OCH_2), 80.0 (br., C-4), 163.2 (br., C-5, C=O), 163.34 (s, C-3), 170.53 (m, C-1). *Anal.* Calcd. for $C_{10}H_{15}N_3O_3S$ (254.31) : C, 46.68; H, 5.88; N, 16.33; S, 12.46. Found: C, 46.79; H, 5.93; N, 16.02; S, 12.45

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