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N-Cyanochloroacetamidine - a Convenient Reagent for the Regioselective Synthesis of Fused Diaminopyrimidines.

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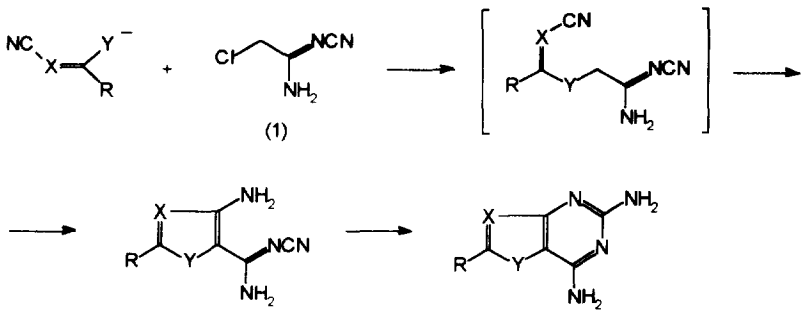
Abstract: *N*-Cyanochloroacetamidin reacts wit conjugated thiolato(selenolato)nitriles to give product of regioselective S(Se) alkylation that can subsequently be involved in the Thorpe reaction. Resulting enaminocyanamidines form pyrimidine rings under acid or base catalysis forming fused diaminopyrimidines. According to this common scheme, functionally substituted thieno[3,2-*d*]pyrimidines, thiazolo[4,5-*d*]pyrimidines, pyrimido[4",5":4',5']thieno[3',2':4,5]thieno[3,2-*d*]pyrimidine, pyrido[3',2':4,5]thieno(selenopheno)[3,2-*d*]pyrimidines, their hydrogenated analogues, and pyrimido-[4',5':4,5]thieno[2,3-*d*]pyrimidine were synthesized.

Substituted thieno- and thiazolopyrimidines reveal different types of biological activity. Within this class there are compounds that are active against pneumonia and toxicosis[1] and analgetics.[2,3] The common method of synthesis of these compounds includes preliminary preparation of 3-amino-2-cyano(ethoxycarbonyl, carbamoyl)thiophenes or the corresponding thiazoles with subsequent condensation with formamide, nitriles or diethyl oxalate.[1,4-7] The same compounds can also be obtained by ring interconversion of thienooxazines with amines or hydrazine.[8]

For the regioselective synthesis of thieno(selenopheno)- or thiazolopyrimidines we propose *N*-cyanochloroacetamidine (1) as a convenient reagent. *N*-Cyanochloroacetamidine (1) was prepared for the first time in 1963.[9] However, until now only a few papers on the synthetic applications of this reagent have been published. In one group of articles, it appears as the alkylating reagent in S_N-reactions;[10,11] in a second group, the cyanamidine moiety was used for closure of the triazine ring, the chlorine atom being retained.[12,13] However, no reactions that affect more than one of the functional groups of this reagent has been described so far.

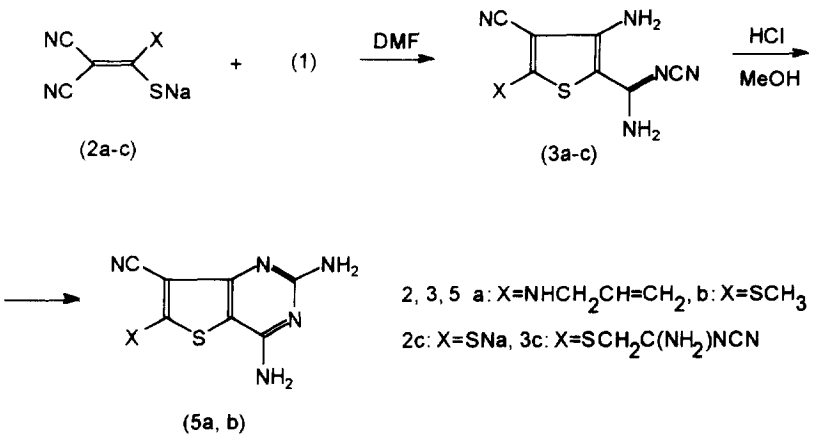
We now report a new convenient method for the synthesis of fused diaminopyrimidines from functionally substituted vicinal unsaturated thiolato(selenolato)nitriles and *N*-cyanochloroacetamidine. Synthesis of the fused pyrimidines was performed according to the following scheme:



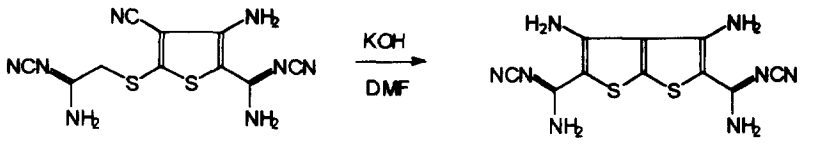
X=N, CR' ; Y=S, Se

Initially, regioselective alkylation of thiolate(selenolate) at the S(Se)-atom with formation of an acyclic product takes place. The latter than undergoes a Thorpe cyclization yielding the aminothiophene or -thiazole ring. Resulting substituted thiophene or thiazole closes the diaminopyrimidine ring under acid or base catalysis.

Sodium 1-allylamino-2,2-dicyanoethylene-1-thiolate (2a), obtained from allylisothiocyanate and malononitrile,[14] reacts with (1) in DMF at room temperature with formation of the substituted thiophene (3a). Analogously, sodium 1-methylthio-2,2-dicyanoethylene-1-thiolate (2b), obtained *in situ* from 2,2-dicyanoethylene-1,1-dithiolate (2c) and methyl iodide,[15] yielded thiophene (3b):

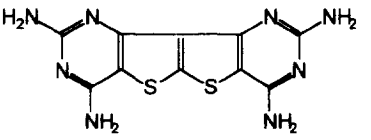


Attempted isolation of an acyclic product failed under these conditions, probably, due to the high electrophilicity of the nitrile carbon atom. The aromatic nitrile group appears to be considerably less reactive in the Thorpe reaction, which was confirmed by reaction of (2c) with two equivalents of (1). Thus only one cyclization takes place at room temperature in DMF yielding thiophene (3c), and closure of two thiophene rings can be achieved by treatment of compound (3c) with a catalytic amount of base:



(3c) (4)

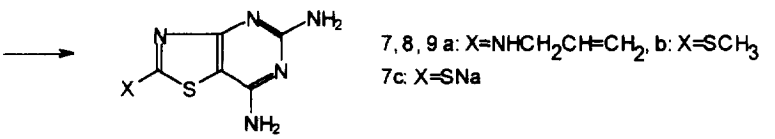
Heating of thiophenes (3a,b) in the methyl alcohol in the presence of HCl results in the closure of the pyrimidine ring as occurred in the formation of thienopyrimidines (5a,b). Analogously, pyrimidothieno-thienopyrimidine (6) was prepared from thienothiophene (4).



(6)

The sodium salt of 1-allyl-3-cyanothiourea (7a), obtained from cyanamide and allylisothiocyanate,[16] reacts with (1) in DMF at room temperature forming the substituted thiazole (8a). Analogously, cyaniminomethylthiocarbothiolate (7b), obtained *in situ* from sodium cyaniminocarbodithiolate (7c) and methyl iodide, reacts to yield thiazole (8b):

(7a, b) (8a, b)

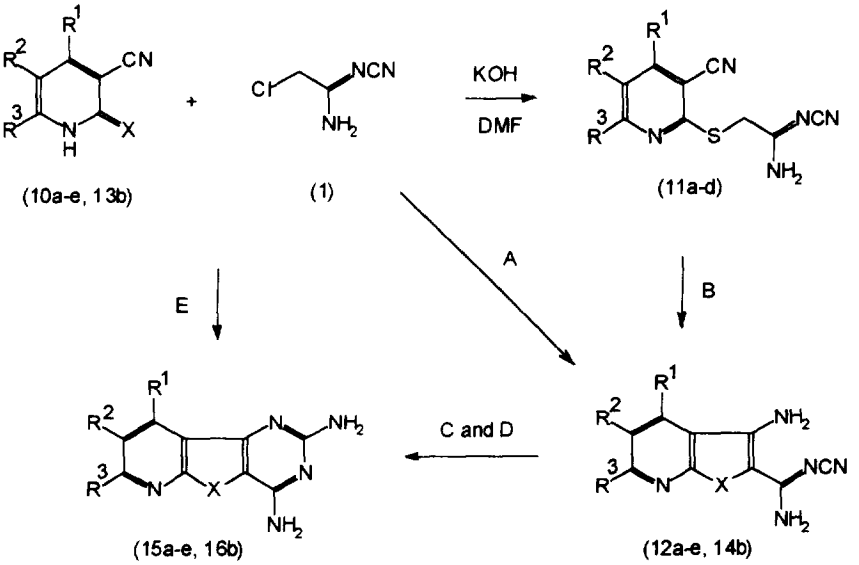


(9a, b)

As in the case of the thiophenes, isolation of acyclic products failed.

Under treatment with HCl in MeOH thiazoles (8a,b) close the diaminopyrimidine ring with formation of thiazolopyrimidines (9a,b) which are of significant interest, because they are thio-analogues of purines.

3-Cyanopyridin-2-thiolates, obtained *in situ* from pyridinethiones (10a-d) and KOH, react with (1) yielding *S*-alkyl products (11a-d). Isolation of acyclic products in this case may be explaned by the considerably lower electrophilicity of the nitrile carbon atom than that of the thiophenes and thiazoles:

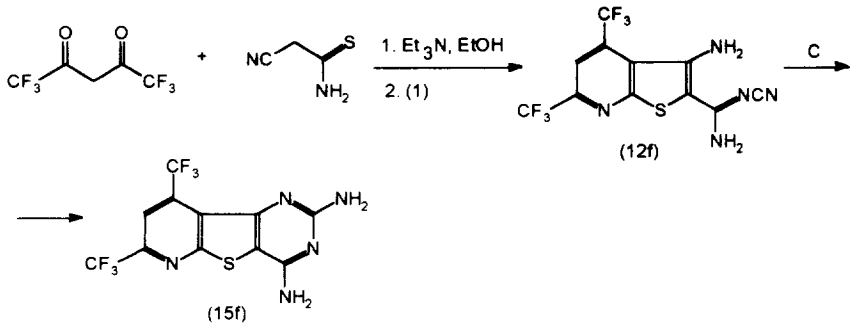


(10a-e, 13b) (1) (11a-d) (15a-e, 16b) (12a-e, 14b)

10, 11, 12, 15 X=S; 13, 14, 16 X=Se

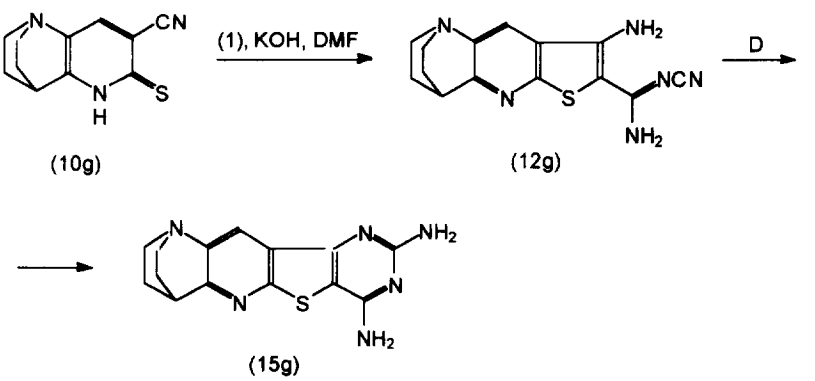
10-16 a: $R^1=R^2=H$, $R^3=CH_3$; b: $R^1=R^3=CH_3$, $R^2=H$; c: R^1=2-Furyl, $R^2=H$, $R^3=CH_3$;
d: R^1=SCH, R^2=CN, $R^3=NH_2$; e: R^1=3-Py, $R^2R^3=(CH_2)_4$

In the presence of excess of KOH, the reaction proceeds further and leads to thienopyridines (12a-d) (Method A), which were also prepared from compounds (11) in DMF by the action of a catalytic amount of base (Method B). In the case of 4-(3-pyridyl)-pyridinethione (10e) the isolation of acyclic product failed, probably because of the catalytic action of the basic substituent. Analogously, the isolation of such a product failed in the case of pyridinselenone (13b) due to immediate formation of selenophenopyridine (14b). This may be caused by the increase of the CH-acidity of the CH -group for $SeCH_2$ as compared to SCH_2. Bis(trifluoromethyl)- substituted compound (12f) was also prepared; the corresponding labile pyridinethione was prepared *in situ*:

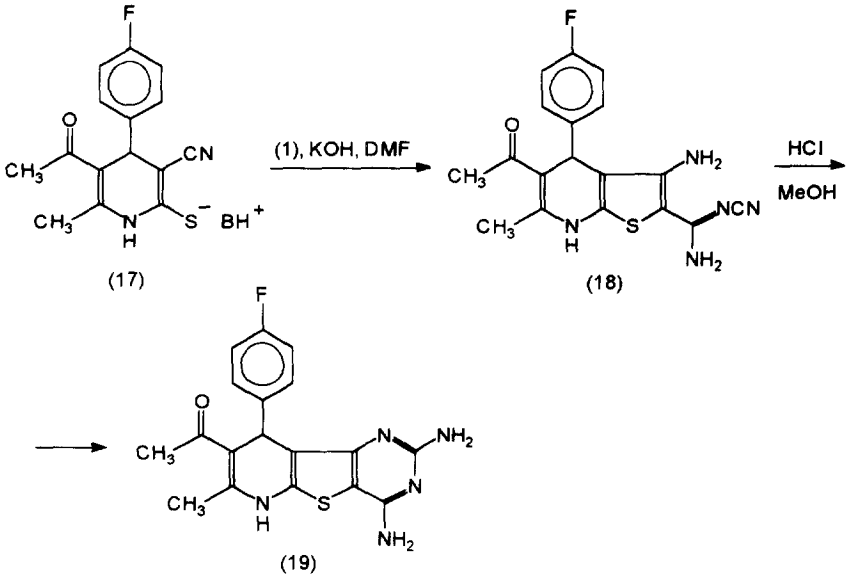


Thieno(selenopheno)pyridines (12a-e, 14b) close the pyrimidine ring both in the conditions of acid (HCl) and base (EtONa/EtOH) catalysis (Methods C and D, correspondingly) with formation of pyridothieno(selenopheno)pyrimidines (15a-e, 16b). Both the furyl substituent in compound (12c) and the functional groups in compound (12d) appeared to be stable in the reaction conditions. The similarity of conditions there thienopyridines (12) are obtained and there their cyclization enables the one-step synthesis of pyridothienopyrimidines (15) from pyridinthiones (10). Such reaction was carried out with dimethyl-substituted compound (10b) (Method E).

Analogous products were obtained from quinuclidine derivative (10g). As in the case of the pyridyl-substituted compound, isolation of acyclic product failed:

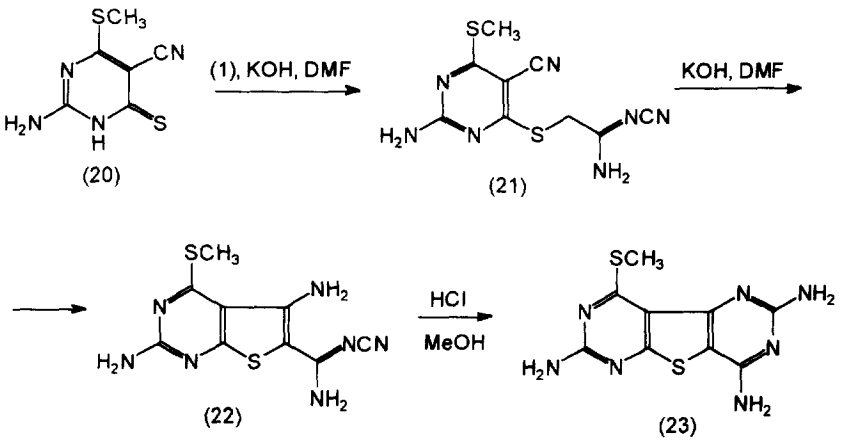


3-Cyano-1,4-dihydropyridine-2-thiolate (17) reacts with (1) in DMF in the presense of equimolar amount of KOH with formation of hydrogenated thienopyridine (18), which closes the pyrimidine ring in acidic conditions yielding hydrogenated pyridothienopyrimidine (19). In this case, stability of the hydrogenated structure would allow one to synthesize new compounds which possess a cardiotonic activity.



B=morpholine

3-Cyano-2(1H)-pyrimidinethione (20) reacts with*N*-cyanochloroacetamidine (1), according to the common scheme, forming pyrimidine (21), thienopyrimidine (22), and pyrimidothienopyrimidine (23) consecutively, thus opening the way to the synthesis of differentfunctionally-substituted bipyrimidines.



Yields and characteristics of prepared compounds are presented in tables 1-3.

IR-Spectra appeared to be the most informative for the establishment of prepared compound structures. Thus, in the acyclic compounds (11a-d, 21) two characteristic bands of CN-groups - at 2225-2215 cm^{-1} (m.,

aromatic CN) and 2190-2170 cm^{-1} (s., amidine CN) are observed. In the thiophenes and thiazoles (3, 4, 8, 12, 14, 18, 22) the former disappears and two bands appear instead of the latter - at 2200-2180 cm and at 2150-2140 cm . This phenomenon is obviously due to the increase of conjugation in cyanamidine group.[9] Both bands disappear after the closure of pyrimidine ring. The chemical shifts of protons of NH_2-groups in H NMR-spectra of such compounds are also characteristic. The amino group in the spectra of compounds (11a-d) appear as the sharp singlet at 8.6-8.7 ppm. In the 3-aminothieno(selenopheno)pyridines (12, 14) the signals of amidine NH_2-group protons are in the area of 8.0-8.2 ppm and the signal of the 3-NH_2 group for the different compounds appear at 6.0-7.8ppm. Both signals appear as poorly resolved dublets. Under the closure of pyrimidine ring the signals are moved in the strong field and appear at 6.9-7.1 (4-NH_2) and at 5.2-6.1 ppm (2-NH_2). However, in the case of thiophenes and thiazoles (3-9) the chemical shifts of amino groups are not so characteristic and strongly depend on the structure and substituents of compounds.

Methyl groups in compound (15b) in ^1H NMR spectra appear as two singlets at 2.55 and 2.90 ppm. By comparison of this spectrum with that of the monomethyl-substituted compound (15a), these signals were assigned to CH_3-groups in positions 7 and 9, respectivly. The opposite attachment was established for the dimethylpyridinthione (10b),[17] thus giving evidence for the cosiderable hindrance of substituent R^1 in compounds (15). Group R^1 makes considerable sterical hinderance as was confirmed by Stewart-Brigleb models. The difference of melting points of compounds (15a) and (15b) may be due to this matter. In the case of furyl-substituted compounds (12c, 15c) such hindarence is displayed by the unusual chemical shifts of 3-H in furan ring. Thus, in compound (12c) the signal of this proton appears at 7.15 ppm while in compound (15c), at 9.08 ppm. Such strong shift in the weak field (~2 ppm) may be due to turn of the furan ring under the influence of sterical hindrance so that the proton in position 3 appears to be hindered by the circle current of the common heterocyclic system.

Thus, we have shown a new common regioselective method for the synthesis of functionally substituted diaminothieno(thiazolo)pyrimidines using conjugated thiolatonitriles and *N*-cyanochloroacetamidine.

EXPERIMENTAL

IR-Spectra were recorded in discs of KBr on Specord-M80, H NMR-spectra - on Bruker WM250 (250 MHz) in DMSO-D_6 solutions, mass-spectra - on Varian Mat CH-6 (70 eV). Elemental analysis was obtained on Perkin-Elmer C,H,N-analyser (obtained data were in agree with calculated). Yields and characteristics of obtained compounds are presented in the tables 1-3.

Starting materials were prepared by described methods: (1)[9], (2a)[14], (2b)[15], (7a)[16], (7b)[18], (10a-c,e,g)[19,20], (10d)[21], (13b)[22], (17)[23], (20)[24], respectively.

Table 1. 2-Amino-2-cyaniminoethylthio-derivatives

Compound	Molecular formula	mp, °C	IR-spectrum, ν, cm^{-1}	H^1 NMR-spectrum, ppm (J, Hz)	Yield, %
3c	$C_{10}H_8N_8S_2$	232-233	3400,3328,3180 (NH_2);2230,2188 2183,2166(CN)	3.92 (br.s., 2H, CH_2), 7.24 (br.s., 2H, 3-NH_2), 8.28 (br.s., 2H, NH_2 of cyanamidine group), 8.63 (br.s., 2H, NH_2 of aminocyaniminoethyl-thio group)	92
11a	$C_{10}H_9N_5S$	191-192	3312,3168(NH_2); 2224,2186(CN)	2.54 (s., 3H, CH_3), 4.22 (br.s., 2H, CH_2) ,7.23 (d., J=8,1H, H5), 8.13 (d., J=8, 1H, H4), 8.57 (br.s., 2H, NH_2)	80
11b	$C_{11}H_{11}N_5S$	195-197	3308,3164(NH_2), 2224,2186(CN)	2.42 (s., 3H, 4-CH_3), 2.50 (s., 3H, 6-CH_3), 4.22 (br.s., 2H, CH_2), 7.14 (s., 1H, H5), 8.58 (br.s., 2H, NH_2)	53
11c	$C_{14}H_{11}N_5OS$	222-223	3304,3160(NH_2); 2216,2182(CN)	2.56 (s., 3H, CH_3), 4.23 (br.s., 2H, CH_2), 6.82 (d.-d., J_1 =1.8, J_2=3.6, 1H, H4-furyl), 7.52 (d., J=3.6, 1H, H3-furyl), 7.57 (s., 1H, H5), 8.07 (d., J=1.8, 1H, H5-furyl), 8.59 (br.s., 2H, NH_2)	30
11d	$C_{11}H_9N_7S_2$	206-207	3372,3208(NH_2); 2218,2182(CN)	2.75 (s., 3H, CH_3), 4.09 (br.s., 2H, CH_2), 7.85 and 7.88 (two br.s., 2H, 6-NH_2),8.80 (br.s., 2H, amidine NH_2)	84
21	$C_9H_9N_7S_2$	209-210	3448,3332,3208 (NH_2);2208, 2170(CN)	2.53 (s., 3H, CH_3), 4.11 (br.s., 2H, CH_2), 7.77 and 7.95 (two br.s., 2H, 2-NH_2), 8.69 (br.s., 2H, amidine NH_2)	95

Table 2. Aminocyaniminomethyl-derivatives

Compound	Molecular formula	mp, °C	IR-spectrum, ν, cm^{-1}	H^1 NMR-spectrum, ppm (J, Hz)	Yield, %
1	2	3	4	5	6
3a	$C_{10}H_{10}N_6S$	223-224	3428,3392,3304, 3216(NH_2);2206, 2178,2146(CN)	3.82, 5.20, 5.25 and 5.83 (allyl), 7.22 (br.s., 2H, 3-NH_2), 7.44 (br.s., 2H, amidine NH_2), 8.22(s.,1H, NH)	73
3b	$C_8H_7N_5S_2$	238-240	3440,3324,3228 (NH_2);2220,2196, 2170(CN)	2.70 (s., 3H, CH_3), 7.27 (br.s., 2H, NH_2), 8.14 (br.s., 2H, amidine NH_2)	71
4	$C_{10}H_8N_8S_2$	>340	3436,3296,3172 (NH_2);2192,2150 (CN)	7.55 (br.s., 4H,3- and 4-NH_2), 7.88 (br.s., 4H, amidine NH_2)	83
8a	$C_8H_{10}N_6S$	228-229	3464,3368,3192 (NH_2);2176,2138 (CN)	3.87, 5.13, 5.19 and 5.85 (allyl), 7.11 (br.s., 2H, 4-NH_2), 7.36 (br.s., 2H, amidine NH_2), 8.65 (s., 1H, NH)	68
8b	$C_6H_7N_5S_2$	228-230	3372,3268,3196 (NH_2);2184,2140 (CN)	2.66 (s., 3H, CH_3), 7.44 (br.s., 2H, 4-NH_2), 7.87 (br.s, 2H, amidine NH_2)	65
12a	$C_{10}H_9N_5S$	253-254	3425,3380,3276, 3148(NH_2);2180, 2150(CN)	2.57 (s., 3H, CH_3), 7.32 (d., J=9, 1H, H5), 7.66 (br.s., 2H, 3-NH_2), 8.01 (br.s., 2H, amidine NH_2), 8.36 (d., J=9, 1H, H4)	92[1] 84[2]
12b	$C_{11}H_{11}N_5S$	269-270	3456,3384,3308, 3168(NH_2);2188, 2140(CN)	2.50 (s., 3H, 6-CH_3), 2.72 (s., 3H, 4-CH_3), 7.06 (s., 1H, H5), 7.23 and 7.27 (two br.s., 2H, 3-NH_2), 8.06 (br.s, 2H,amidine NH_2)	88[1] 96[2]
12c	$C_{14}H_{11}N_5OS$	247-248	3456,3320,3160 (NH_2);2200,2148 (CN)	2.60 (s., 3H, CH_3), 6.78 (d.-d., J_1=1.9, J_2=3.2, 1H, H4 furyl), 7.15 (d., J=3.2, 1H, H3 furyl), 7.20 (br.s., 2H,3-NH_2), 7.44 (s., 1H, H5), 8.02 (d., J=1.9, 1H, H5 furyl), 8.15 (br.s., 2H, amidine NH_2)	47
12d	$C_{11}H_9N_7S_2$	228-229	3470,3340,3152 (NH_2);2220,2180, 2140(CN)	2.74 (s., 3H, CH_3), 7.57 and 7.59(two br.s., 2H, 3-NH_2),7.80 and 7.83(two br.s., 2H, 6-NH_2), 8.32 (br.s., 2H, amidine NH_2)	78

Table 2. Continuation

1	2	3	4	5	6
12e	$C_{18}H_{16}N_6S$	246-247	3488,3312,3156 (NH_2);2185,2140 (CN)	1.60-1.74 and 1.74-1.86 (two m., 2x2H, $2CH_2$), 2.44 (t., J=6, 2H, 5-CH_2), 3.01 (t., J=6, 2H, 6-CH_2), 5.91 (br.s., 2H, 3-NH_2), 7.62 (d.-d., J_1=8, J_2=5, 1H, 5H pyridyl), 7.86 (d.-t.,J_1=8, J_2=2, 1H, 4H pyridyl), 8.10 (br.s., 2H, amidine NH_2), 8.58 (d., J=2, 1H, 2H pyridyl), 8.77 (d-d., J_1=5, J_2=2, 1H, H6 pyridyl)	89
12f	$C_{11}H_5F_6N_5S$	244-245	3504,3452,3312, 3184(NH_2);2198, 2160(CN)	7.08 (br.s., 2H, 3-NH_2), 8.22 (s., 1H, H5), 8.70 (br.s., 2H, amidine NH_2)	57
12g	$C_{14}H_{14}N_6S$	301-302	3392,3276(NH_2); 2182,2142(CN)	1.80, 2.22, 3.16 and 3.71 (four m., 4x2H, CH_2), 3.2-3.4 (CH)[3], 7.87 (br.s., 2H, 3-NH_2), 8.18 (br.s., 2H, amidine NH_2), 8.65 (s., 1H, H4)	85
14b	$C_{11}H_{11}N_5Se$	237-239	3420,3296,3176 (NH_2);2180,2130 (CN)	2.50 (s., 3H,6-CH_3), 2.72 (s., 3H, 4-CH_3), 7.08, (s., 1H, H5), 7.43 (br.s., 2H, 3-NH_2), 7.90 (br.s., 2H, amidine NH_2)	53
18[4]	$C_8H_{16}FN_5O$ $S{\cdot}C_3H_7NO$	196-197	3452,3324,3180 (NH_2);2178,2138 (CN)	2.12 (s., 3H, 6-CH_3), 2.31 (s., 3H, CH_3CO), 5.17 (s., 1H, H4), 6.98 (br.s., 2H, 3-NH_2), 7.05 (t., J=9, 2H, H3 Ar), 7.32 (d.-d., J_1=9, J_2=5.5, 2H, H2 Ar), 7.39 (br.s., 2H, amidine NH_2), 10.07 (s., 1H, NH)	81
22	$C_9H_9N_7S_2$	271-272	3420,3308,3196 (NH_2);2184,2145 (CN)	2.63 (s., 3H, CH_3), 6.90 (br.s., 2H, 3-NH_2), 7.24 and 7.28 (two br.s., 2H, 6-NH_2), 7.77 (br.s., 2H, amidine NH_2)	82

[1]Method A, [2]Method B, [3]Overlaps with another signal, [4]Contains DMF

Table 3. Fused Diaminopyrimidines

Compound	Molecular formula	mp, °C	IR-spectrum, ν, cm^{-1}	H^1 NMR-spectrum, ppm (J, Hz)	Yield, %
1	2	3	4	5	6
5a	$C_{10}H_{10}N_6S$	>340	3390,3100(NH_2); 2212(CN)	3.97, 5.25, 5.29 and 5.87(allyl), 7.56 (br.s., 2H, 2-NH_2), 8.28 (br.s., 2H, 4-NH_2), 9.62 (s., 1H, NH)	82
5b	$C_8H_7N_5S_2$	>340	3468,3312,3076 (NH_2);2214(CN)	2.76 (s, 3H, CH_3), 6.72 (br.s., 2H, 2-NH_2), 7.16 (br.s., 2H, 4-NH_2)	93
6	$C_{10}H_8N_8S_2$	>340	3308,3144(NH_2)	7.22 (br.s., 4H, 2- and 9-NH_2), 7.87 (br.s., 4H, 4- and 7-NH_2)	86
9a	$C_8H_{10}N_6S$	272-275	3380,3312,3136 (NH)	3.95, 5.14, 5.22 and 5.87(allyl), 7.48 (br.s., 2H, 2-NH_2), 8.06 (br.s., 2H, 4-NH_2), 9.68 (s., 1H, NH)	78
9b	$C_6H_7N_5S_2$	289-291	3356,3315,3140 (NH_2)	2.80 (s., 3H, CH_3), 6.04 (br.s., 2H, 2-NH_2), 7.00 (br.s., 2H, 4-NH_2)	84
15a	$C_{10}H_9N_5S$	>340	3472,3316,3164 (NH_2)	2.62 (s., 3H, CH_3), 6.14 (br.s., 2H, 2-NH_2), 7.05 (br.s., 2H, 4-NH_2), 7.36 (d., J=8, 1H, H8), 8.25 (d., J=8, 1H, H9)	76
15b	$C_{11}H_{11}N_5S$	298-299	3464,3424,3328, 3204(NH_2)	2.55 (s., 3H, 7-CH_3), 2.90 (s., 3H, 9-CH_3), 5.96 (br.s., 2H, 2-NH_2), 6.92 (br.s., 2H, 4-NH_2), 7.12 (s., 1H, H8)	91[1] 93[2] 70[3]
15c	$C_{14}H_{11}N_5OS$	252-254	3464,3320,3124 (NH_2)	2.63 (s., 3H, CH_3), 6.15 (br.s., 2H, 2-NH_2), 6.69 (d.-d., J_1=1.5, J_2=3.6, 1H, H4 furyl), 7.01 (br.s., 2H, 4-NH), 7.73 (s., 1H, H8), 7.93 (d., J=1.5, 1H, H5 furyl), 9.08 (d., J=3.6, 1H, H3 furyl)	79
15d	$C_{11}H_9N_7S_2$	254-255	3404,3320,3224, 3084(NH_2);2212 (CN)	2.64 (s., 3H, CH_3), 6.71 (br.s., 2H, 2-NH_2), 6.94 (br.s., 2H, 7-NH_2), 7.42 (br.s., 2H, 4-NH_2)	73
15e	$C_{18}H_{16}N_6S$	314-316	3460,3324,3108 (NH_2)	1.65-1.77, 1.77-192 (two m., 2x2H, CH_2), 2.46 (t., J=6, 2H, 8-CH_2), 3.04 (t., J=6 ,2H, 7-CH_2), 5.22 (br.s., 2H, 2-NH_2), 6.93 (br.s., 2H, 4-NH_2), 7.47 (d.-d., J_1=8, J_2=5, 1H, 5H pyridyl), 7.70 (d.-t., J_1=8, J_2=2, 1H, 4H pyridyl), 8.41 (d., J=2, 1H, 2H pyridyl), 8.61 (d.-d., J_1=5, J_2=2, 1H, 6H pyridyl)	85

Table 3. Continuation

1	2	3	4	5	6
15f	$C_{11}H_5F_6N_5S$	249-250	3560,3452,3324, 3168(NH_2)	7.37 (s., 1H, H8), 6.18 (br.s., 2H, 2-NH_2), 7.37 (br.s., 2H, 4-NH_2)	74
15g	$C_{14}H_{14}N_6S$	>340	3420,3336,3172 (NH_2)	1.62, 2.00, 2.58 and 3.17(four m., 4x2H, CH_2), 3.2-3.4 (CH)[4], 6.12 (br.s., 2H, 2-NH_2), 7.06 (br.s., 2H, 4-NH_2), 7.89 (s., 1H, H9)	84
16b	$C_{11}H_{11}N_5Se$	288-289	3492,3340,3132 (NH_2)	2.52 (s., 3H, 7-CH_3), 2.88 (s., 3H, 9CH_3), 5.90 (br.s., 2H, 2-NH_2), 6.78 (br.s., 2H, 4-NH_2), 7.11 (s., 1H, H8)	76
19	$C_8H_{16}FN_5OS$	216-217	3324,3208(NH_2); 1648(CO)	2.8 (s., 3H, 7-CH_3), 2.38 (s., 3H, CH_3CO), 5.32 (s., 1H, H9), 5.80 (br.s., 2H, 2-NH_2), 6.57 (br.s., 2H, 4-NH_2), 7.01 (t., J=8.5, 2H, H3 Ar), 7.38 (d.-d., J_1=5.5, J_2=8.5, H2 Ar), 10.04 (s., 1H, NH)	80
23	$C_9H_9N_7S_2$	>340	3420,3332,3168 (NH_2)	2.50 (s.,3H,CH_3), 5.90 (br.s., 2H,2-NH_2), 6.35 (br.s., 2H, 7-NH_2), 6.55 (br.s., 2H, 4-NH_2)	70

[1]Method C, [2]Method D, [3]Method E, [4]Overlaps with another signal

5-Allylamino-3-amino-2-(aminocyaniminomethyl)-4-cyanothiophene (3a) and 2-allylamino-4-amino-5-(aminocyaniminomethyl)thiazole (8a)

To a solution of 10 mmol of thiolate (2a, 7a) in 5ml DMF a 10.1 mmol of N-cyanochloroacetamidine (1) was added and the resulting mixture was allowed to stand for 3h at the room temperature. After which the product of reaction was precipitated with water, filtered off, washed with alcohol and dried in the air.

3-Amino-2-(aminocyaniminomethyl)-4-cyano-5-methylthiothiophene (3b) and 4-amino-5-(amino-cyaniminomethyl)-2-methylthiothiazole (8b)

To a solution of 10 mmol of dithiolate (2c, 7b) in 5 ml DMF a 10 mmol of methyliodide was added and the mixture was allowed to stand for 0.5h. After which a 10 mmol of (1) was added and the mixture keept for another 3h. The reaction mixture was decomposed with water and the product was isolated as described above.

3-Amino-2-(aminocyaniminomethyl)-5-(2-amino-2-cyaniminoethylthio)-4-cyanothiophene (3c)

To a solution of 5 mmol of dithiolate (2c) in 5 ml DMF 10.2 mmol of (1) was added and the mixture was allowed to stand for 3h at the room temperature. The product was isolated as described above.

2-(2-Amino-2-cyaniminoethylthio)-3-cyanopyridines (11a-d) and 4-(2-amino-2-cyaniminoethyl-thio)-5-cyano-6-methylthiopyrimidine (21)

To a solution of 3 mmol of thione (10a-d, 20) in 20 ml DMF, 2.8 mmol of KOH (10% aqueous solution) was added, the reaction mixture was stirred for 5min at room temperature, after which 3 mmol of (1) was added. In 5min the product was precipitated with water, filtered off, washed with alcohol and dried in air.

(11b) ^{13}C NMR-spectrum, ppm: 9.9 (4-CH_3), 14.4 (6-CH_3), 21.7 (CH_2), 94.1 (amidine-CN), 105.2 (C3), 111.2 (C5), 112.6 (3-CN),143.0 (C6), 151.9 (C4), 155.8 (C2), 163.5 (amidine-C)

(11b) Mass-spectrum, m/e (intensity, %): 247 (6), 246 (16), 245 (100, M^+), 228 (22, M^+- NH_2), 212 (42, M^+-SH), 203 (23, M^+- H_2NCN)

3-Amino-2-aminocyaniminomethylthieno(selenopheno)[2,3-b]pyridines (12a-e,g, 14b) and 6-aminocyaniminomethyl-3,7-diamino-1-methylthio-thieno[2,3-d]pyrimidine (22) from thiones (10a-e,g, 13b, 20) (Method A)

To a solution of 3 mmol of thione (10a-e,g, 20) or selenone (13b) in 20 ml DMF 3 mmol of KOH (10% aqueous solution) was added and the mixture was stirred for 5 min, a 3.1 mmol of (1) was added, and the mixture stirred for an additional 5 min. After which another 6 mmol of KOH was added and stirred for 0.5h. The product was precipitated with water, washed with alcohol and recrystallized from CH_3CN.

(12b) ^{13}C NMR-spectrum, ppm: 10.3 (4-CH_3), 14.2 (6-CH_3), 106.3 (C2), 112.5 (C5), 112.9 (CN), 120.6 (C3a), 135.5 (C6), 139.7 (C4), 150.0 (C3), 155.4 (C7a)

(12b) Mass-spectrum, m/e (intensity,%): 247 (13), 246 (34), 245 (100, M^+), 228 (39, M^+-NH_3), 203 (46, M^+-H_2NCN)

3,4-Diamino-2,5-di(aminocyaniminomethyl)thieno[2,3-b]thiophene (4) and 3-amino-2-aminocyaniminomethylthieno[2,3-b]pyridines (12) from pyridines (11) (Method B)

To a solution of 1 mmol of compound (3c, 11a,b) in 10 ml DMF 0.5 mmol of KOH (10% aqueous solution) was added. After standing for 0.5 h at room temperature the product was precipitated with water and treated as described for the Method A.

3-Amino-2-aminocyaniminomethyl-4,6-bistrifluoromethyl-thieno[2,3-b]pyridine (12f)

To a solution of 5 mmol of cyanothioacetamide and 5 mmol of Et_3N in 20 ml of absolute alcohol 5 mmol of hexafluoroacethylacetone was rapidly added. The reaction mixture was allowed to stand for 12h at 20 °C and then 5.1 mmol of (1) was added. After standing for 20 min at 40 °C the mixture was cooled and the precipitated product was treated as described for the Method A.

5-Acetyl-3-amino-2-aminocyaniminomethyl-4,7-dihydro-4-(4-fluorophenyl)-6-methylthieno[2.3-b]pyridine (18)

To a solution of 5 mmol of salt (17) in 10 ml DMF 5 mmol KOH (10% aqueous solution) and 5.1 mmol of (1) were added, consecutively. The mixture was allowed to stand for 0.5 h at room temperature, then water added until some turbibity appeared, and allowed to crystallize for one night. The precipitated product was filtered off, washed with water, and dried in the air.

Closure of the pyrimidine ring in acidic conditions. Thienopyrimidines (5a,b), pyrimidothienothienopyrimidine (6),thiazolopyrimidines (9a,b), pyridothienopyrimidines (15b,f) (Method C), dihydropyridothienopyrimidine (19), and pyrimidothienopyrimidine (23)

A solution of 2 mmol of compounds (3a,b, 8a,b, 12b,f, 18)in 10 ml MeOH containing 3 ml of 35% HCl was stirred at room temperature for 12 h. In the case of poorly soluble compounds (4 and 22) the mixture was boiled for 12 h. After which the mixture was poured in to water and neutralized with Na_2CO_3. The product was isolated as described for (12).

Closure of the pyrimidine ring in basic conditions. 2,4-Diaminopyrido[3',2':4,5]-thieno(seleno-pheno)[3,2-d]pyrimidines (15a-e, 16b) (Method D)

To a solution of 3 mmol Na in 20 ml of alcohol 1 mmol of thieno(selenopheno)pyridine (12, 14) was added. The resulting mixture was boiled for 6 h, then cooled. The precipitated product was isolated as described above for (12)

(15b) ^{13}C NMR-spectrum, ppm: 18.7(7-CH_3), 23.9(9-CH_3), 101.2(C4a), 121.8 (C8), 123.6 (C9a), 146.2 (C7), 157.1 (C9), 158.5 and 158.7 (C2 and C9b), 161.7 and 161.9 (C4 and C5a)

(15b) Mass-spectrum, m/e (intensity, %): 247 (30), 246 (41), 245 (100, M^+), 228 (43, M^+-NH_3), 203 (41, M^+-H_2NCN)

2,4-Diamino-7,9-dimethylpyrido[3',2':4,5]thieno[3,2-d]pyrimidine (15b) from pyridinthione (10b) (Method E)

To a solution of 1 mmol of thione (10b) in 20 ml of alcohol 1 mmol of aqueous KOH was added, the mixture was stirred for 10 min at room temperature. After that 1.1 mmol of *N*-cyanochloroacetamidine (1) was added and allowed to stand for 20 min at room temperature. Then to the reaction mixture a solution of 3 mmol of EtONa in EtOH was added and boiled for 2 h. The product was isolated as described above for (12).

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