Synthesis and hydrolytic cleavage of 1-aryl-5-cyano-6-(2-dimethylaminovinyl)-4-oxo(thioxo)-1,4-dihydropyrimidines

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1-Aryl-5-cyano-6-(2-dimethylaminovinyl)-4-oxo-1,4-dihydropyrimidines and their 4-thioxo analogs, which were prepared in three steps from cyanoacetamide and cyanothioacetamide, respectively, were subjected to hydrolysis. In aqueous AcOH, hydrolysis of *N*-(dimethylaminomethylene)-2-cyano-5-dimethylamino-2,4-pentadieneamide derivatives containing amino groups at position 3 afforded formylpyridones. The reaction of 2-cyano-3-dimethylaminothiocrotonamide with DMF dimethyl acetal gave rise to 3-cyano-4-dimethylamino-2-methylthiopyridine.

Key words: amide acetals, enaminoamides, enaminothioamides, pyrimidines, pyridines, benzo[*b*][1,6]naphthyridines.

Earlier, it has been demonstrated that 2-cyano-3-dimethylaminocrotonamide (**1**) undergoes transamination with aniline[1] and *p*-toluidine[2] to give 3-arylamino-2-cyanocrotonamides (**2a,b**). Condensation of the latter with *N,N*-dimethylformamide diethyl acetal (**3a**) proceeds both at the amide NH_2 group and the activated Me group to form 1-aryl-5-cyano-6-(2-dimethylaminovinyl)-4-oxo-1,4-dihydropyrimidines[1,2] (**4a,b**) (Scheme 1). Hydrolytic cleavage of the pyrimidine ring in molecule **4a** was found to be accompanied by recyclization. In an alkaline medium,[3] the reaction afforded 4-anilino-3-cyano-2-oxo-1,2-dihydropyridine (**6a**). In an acidic medium (90% aqueous AcOH at room temperature),[4] the reaction gave rise to a mixture of pyridone **6a** and 4-anilino-3-cyano-5-formyl-2-oxo-1,2-dihydropyridine (**7a**).

However, when reproducing a procedure[2,5] for the synthesis of **4a** from enaminoamides **2a,b**, we obtained mixtures of pyrimidinones **4a,b** and acyclic intermediates **5a,b**. Alkaline hydrolysis of these mixtures afforded only pyridones **6a,b** in good yields, *i.e.*, under alkaline conditions both components of the mixture underwent analogous transformations.

To the contrary, hydrolysis of **4a** + **5a** and **4b** + **5b** mixtures in an acidic medium (90% aqueous AcOH, 20 °C) afforded formyl derivatives **7a,b**, their yields being always lower than the percentage of acyclic forms **5a,b** in the mixtures. Under more severe conditions, condensation of enaminoamides **2a,b** with acetals **3a,b** gave rise to pure pyrimidinones **4a,b**. It appeared that acid hydrolysis of compounds **4a,b** afforded the corresponding pyridones **6a,b** as the major products. After their separation and removal of the solvent *in vacuo*, a number of minor products were found in the reaction mixtures. Based on the results of ^{1}H NMR spectroscopy and mass spectrometry,* isomeric structures **8a**,**b** and **9a,b** were assigned to two of these minor products (Scheme 2). The **6a** : **8a** : **9a** ratio is 10 : 5 : 1 (a similar component ratio was found for a mixture of **6b**, **8b**, and **9b**). The spectra of both pairs of minor products **8a,b** and **9a,b** are characterized by the presence of two doublets of the vinyl protons with $^3J_{H,H}$ = 12.4—12.5 Hz, which is indicative of their *E* configuration. The spectrum of compound **8a** has characteristic signals at δ 6.18 (d, 1 H, H(4), $^3J_{H,H}$ = 12.4 Hz), the corresponding doublet for H(5) overlaps with the signals for the aromatic protons at δ 7.69 (br.s, 1 H, NCHO). The spectrum of compound **9a** has signals at δ 6.78 (d, 1 H, H(4), $^3J_{H,H}$ = 12.4 Hz), 8.15 (d, H(5), $^3J_{H,H}$ = 12.4 Hz), and 7.95 (s, 1 H, amidine CH). An analogous spectral pattern is observed for a **8b** + **9b** mixture. The mass spectra of mixtures containing **8a** and **9a** show signals at *m/z* 285 $[M + H]^+$, 307 $[M + Na]^+$, 569 $[2 M + H]^+$, and 591 $[2 M + Na]^+$. The mass spectra of mixtures containing **8b** and **9b** have signals at *m/z* 299 $[M + H]^+$, 321 $[M + Na]^+$, 597 $[2 M + Na]^+$, and 619 $[2 M + Na]^+$.

Evidently, compounds **8a,b** and **9a,b**, are intermediates for the synthesis of pyridones **6a,b** formed due to the opening of the pyrimidine ring in pyrimidinones **4a,b** at the N(1)—C(2) bond under the action of nucleophilic species present in the reaction medium (Scheme 3);

* Since the mass spectra (EI) of the mixtures containing the above-mentioned products show no M^+ peaks, we used the ESIMS method on a Micromass Autospec electrospray mass spectrometer.

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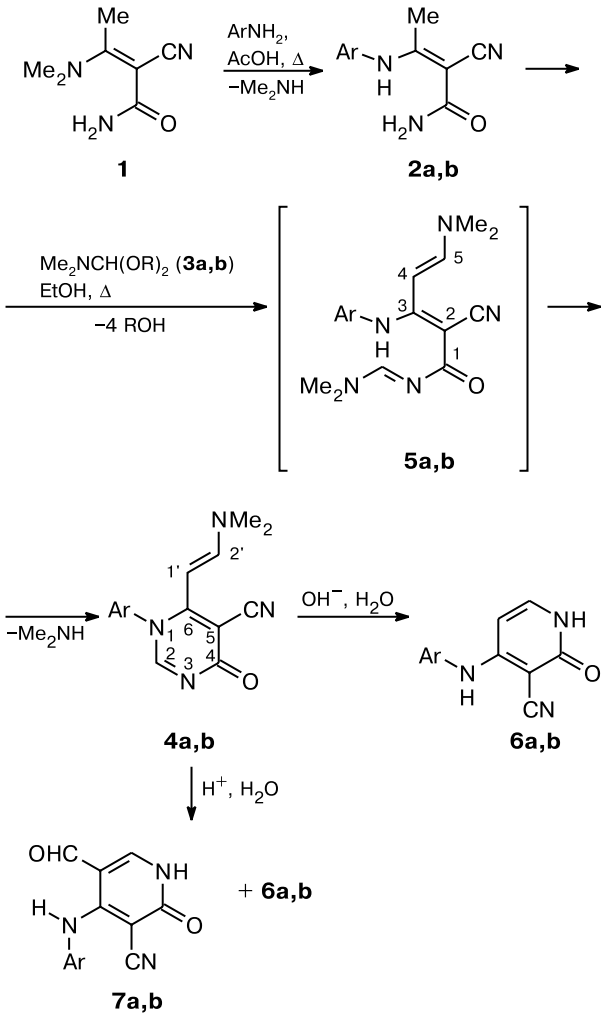
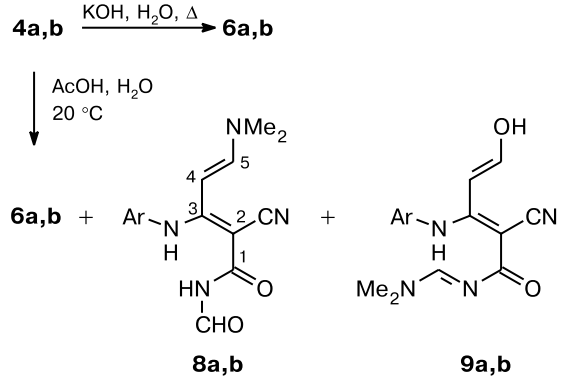
Scheme 1



Ar = Ph (**a**), *p*-MeC_6H_4 (**b**); R = Et (**a**), Me (**b**)

Scheme 2



AcO^- and H_2O as well as $HCOO^-$ and $NHMe_2$, which are generated in the course of transformation of pyrimidinones, could serve as such species. The involvement of dimethylamine in the pyrimidine-ring opening is evident from the structures of compounds **9a,b** containing the dimethylamino group.

It should be emphasized that the ^{1}H NMR and mass spectra of the reaction mixtures did not reveal even traces of aldehydes **7a,b**.

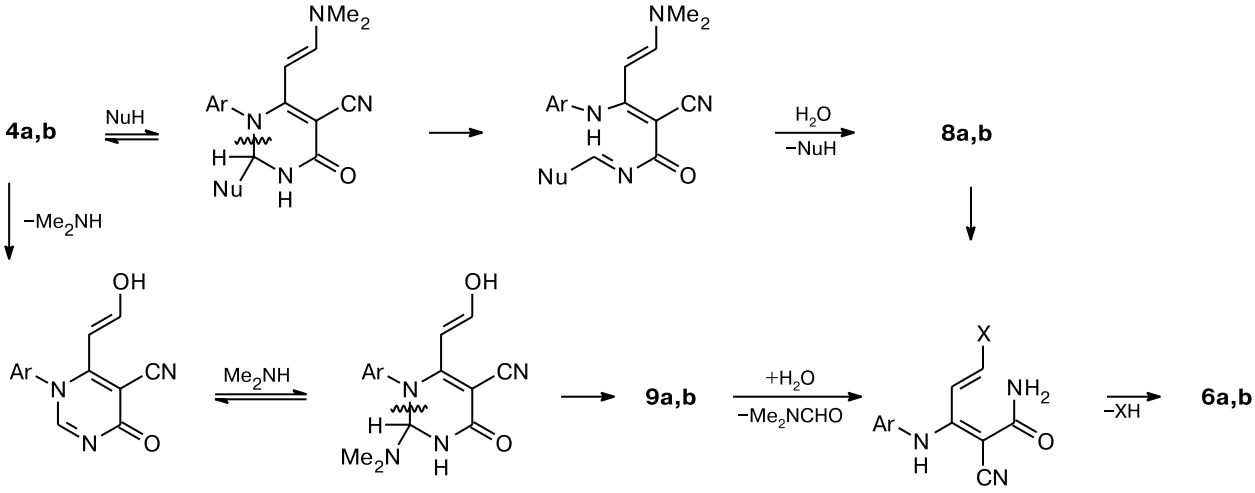
To elucidate the pathways of their formation, we attempted to synthesize acyclic compounds **5a,b** under mild conditions. However, we failed to prepare these compounds in the pure form, because they were readily transformed into the corresponding pyrimidinones **4a,b**. Therefore, we performed the reaction of enamine **1** with acetal **3b** to prepare another dieneamidine, *viz.*, 2-cyano-*N*-dimethylaminomethylene-3,5-bis(dimethylamino)-2,4-pentadieneamide (**10**), as a model compound for studying acid hydrolysis. In compound **10**, the arylamino fragment is replaced with the dimethylamino group, which excludes its cyclization to the corresponding pyrimidinone (Scheme 4). Compound **10** was smoothly transformed into 3-cyano-5-formyl-4-dimethylamino-2-oxo-1,2-dihydropyridine (**11**) in good yield upon treatment with aqueous AcOH at 20 °C.

Therefore, it was demonstrated that hydrolysis of dieneamidines **5a,b** and **10** in an acidic medium afforded formylpyridones **7a,b** and **11**, respectively. Hydrolysis of pyrimidines **4a,b** gave rise exclusively to pyridones **6a,b**. The assumed mechanism of the transformation of dieneamidines **5a,b** and **10** into the corresponding 5-formylpyridones **7a,b** and **11** in an acidic medium involves protonation of the starting compounds at the carbonyl O atom, which is the center of the highest electron density. (The cations generated in this process are stabilized by electron-donating groups.) The subsequent steps of the process are as follows: cyclization involving the β-enamine C atom, elimination of dimethylamine, deprotonation, and hydrolysis of the dimethylaminomethylene group to the formyl group giving rise to aldehydes **7a,b** and **11** (Scheme 5).

It should be noted that refluxing of aldehyde **7b** in $POCl_3$ in the presence of $Et_3N \cdot HCl$ led to the replacement of the oxo group with the chlorine atom and cyclization to form 3-chloro-4-cyano-8-methylbenzo[*b*][1,6]naphthyridine (**12**) (Scheme 6). An analogous transformation of aldehyde **7a** has been described earlier.[5]

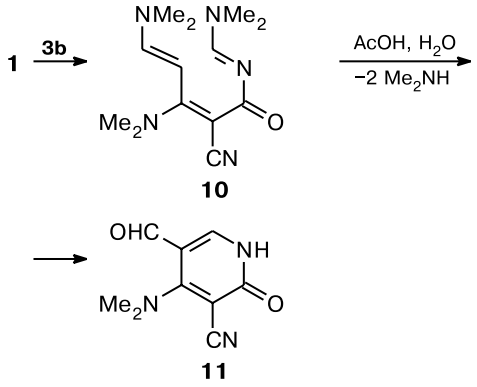
Then we synthesized 1-aryl-5-cyano-6-(2-dimethylaminovinyl)-4-thioxo-1,4-dihydropyrimidines (**13a,b**) and studied hydrolysis and new heterocyclizations involving these compounds. Condensation of cyanothioacetamide with *N,N*-dimethylacetamide dimethyl acetal afforded 2-cyano-3-dimethylaminothiocrotonamide (**14**) (Scheme 7), whose transamination with aniline and *p*-chloroaniline on refluxing in glacial AcOH gave enaminothioamides **15a,b**. In the ^{1}H NMR spectra of these compounds, the signals for the NH protons of the

Scheme 3

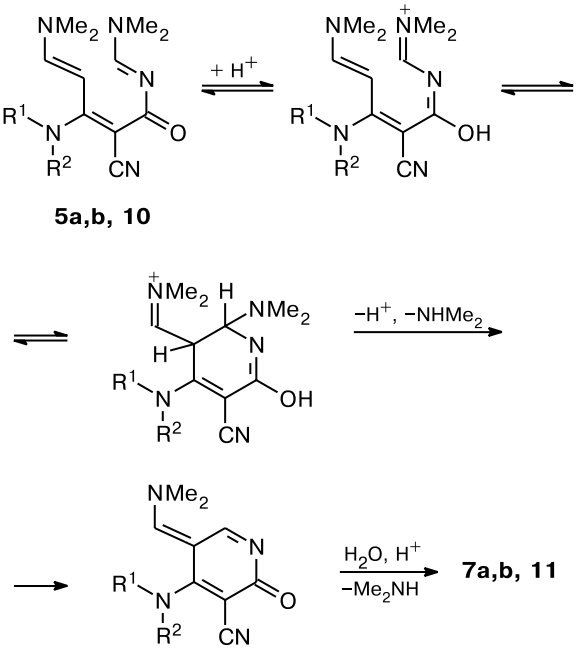


NuH = H_2O, $NHMe_2$, CH_3COOH, HCOOH; X = OH, NMe_2

Scheme 4



Scheme 5

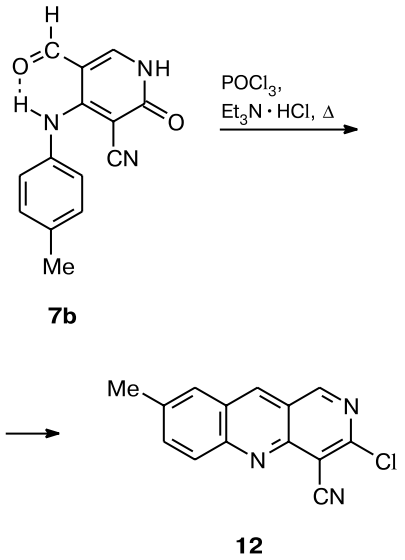


5a, 7a: R^1 = Ph, R^2 = H; **5b, 7b:** R^1 = *p*-MeC_6H_4, R^2 = H; **10, 11:** R^1 = R^2 = Me

arylamino group are observed at very low field, which may be indicative of the presence of a strong intramolecular N—H...S hydrogen bond. The signals for the protons of the thioamide group appear as two broadened singlets, which is indicative of hindered rotation about the C—N bond. Condensation of **15a,b** with an excess of acetal **3b** performed by refluxing in dry toluene over a long period afforded pyrimidinethiones **13a,b**. It should be noted that it is necessary to carry out all three steps of this synthesis under argon because exposure of the reaction mixture to atmospheric oxygen leads to its rapid resinification. The behavior of pyrimidinethiones **13a,b** under conditions of alkaline hydrolysis on refluxing in 1 *M* aqueous KOH was studied. Acidification of the resulting solutions with AcOH gave pyridinethiones **16a,b**. Refluxing of compound **13a** in aqueous KOH, in Pr^iOH with aniline, or in distilled water invariably afforded compound **16a**. Under conditions of acid hydrolysis (treatment with aqueous AcOH at 20 °C under argon), pyrimidinethiones **13a,b** were also transformed into pyridinethiones **16a,b**, although in somewhat lower yields.

It should be noted that attempts to perform hydrolysis (in aqueous AcOH or 1 *M* HCl) of mixtures containing pyrimidinethiones **13** and acyclic compounds **17** (the latter are unstable and cannot be prepared in the individual form) failed. In none of the cases, were pyridinethiones containing the formyl group at position 5 (**18**) de-

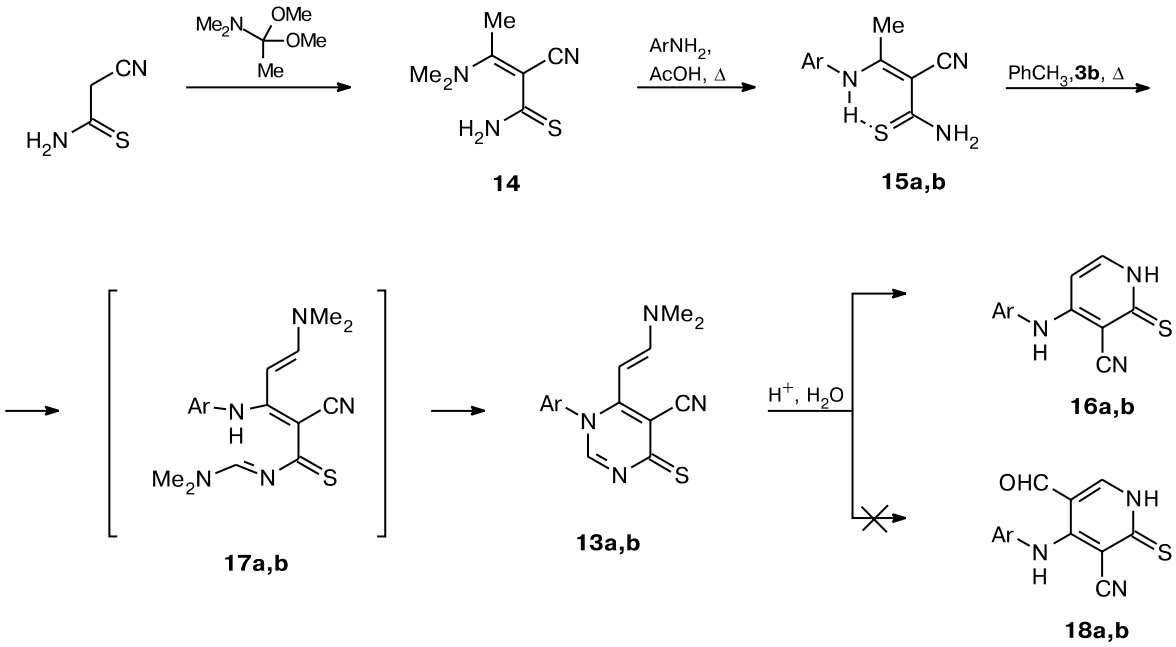
Scheme 6



tected even spectroscopically. Condensation of enaminothioamide **14** with acetal **3b** by refluxing in dry toluene followed by treatment with aqueous AcOH afforded 3-cyano-4-dimethylamino-2-methylthiopyridine (**19**) in moderate yield. The characteristic feature of the latter is the presence of the methylthio group. It is known that amide acetals react with S-nucleophiles to give *S*-alkylation products.[6] Apparently, methylation of the S atom in compound **14** with acetal **3b** proceeds more rapidly than condensation of **14** at the thioamide NH_2 group. After the transformation of the —(C=S)—NH_2 group into —C(MeS)=NH, the acetal can react only at the α-Me group of the enamine fragment resulting in the closure of the pyridine ring to form compound **19** (Scheme 8).

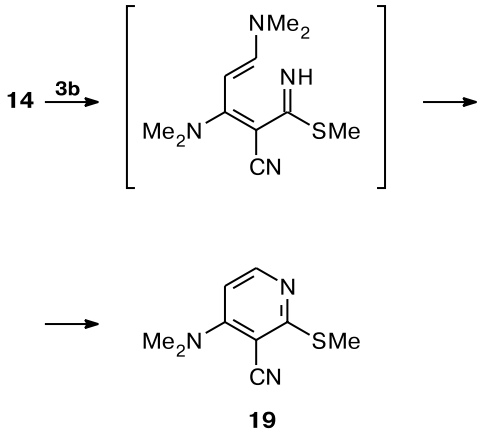
Since attempts to prepare formylpyridinethione (analogous to **7a,b**) from the corresponding pyrimidinethione **13a** failed, we changed the strategy of the synthesis. The introduction of the formyl group at the β position of the enamine fragment of pyrimidinethione **13a** provides a prerequisite for the formation of aldehyde **18**. Taking into account sensitivity of the substrate to an acidic medium as well as strong susceptibility of the pyrimidine ring to the nucleophilic attack, we used carbenium salts, which were generated *in situ* by the reaction of triethyl orthoformate with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −40 °C,[7] as the formylating agent. Judging from the ^1H NMR spectrum, we obtained a mixture containing the starting compound and an acyclic product bearing the ethyl group. Under more severe temperature conditions (refluxing in CH_2Cl_2), the transformation of the starting pyrimidinethione **13a** proceeded much more rapidly. The reaction mixture was concentrated to prepare an oil, whose treatment with aqueous Na_2CO_3 afforded a crystalline product. According to the results of IR spectroscopy, mass spectrometry, ^1H NMR spectroscopy, and the ^1H—^{13}C correlation experiment, this product has the structure of 3-cyano-2-ethylthio-4-

Scheme 7



Ar = Ph (**a**), *p*-ClC_6H_4 (**b**)

Scheme 8

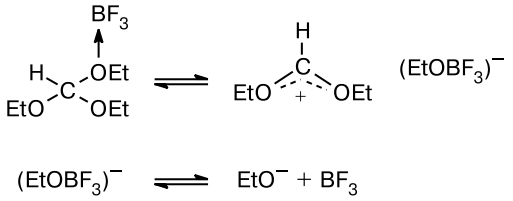


19

formylanilinopyridine (**20**). Presumably, the ethoxide anion generated due to dissociation of the complex of triethyl orthoformate with BF_3 serves as the nucleophilic agent, which provides the pyrimidine-ring opening (Scheme 9).

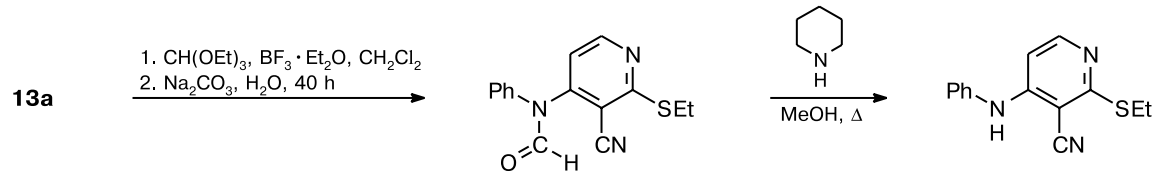
Deformylation of compound **20** was carried out by refluxing with piperidine in methanol to prepare 4-anilino-3-cyano-2-ethylthiopyridine (**21a**) in high yield (Scheme 10). The structure of this compound was established spectroscopically and by the independent synthesis from pyridinethione **16a** (Scheme 11).

Scheme 9

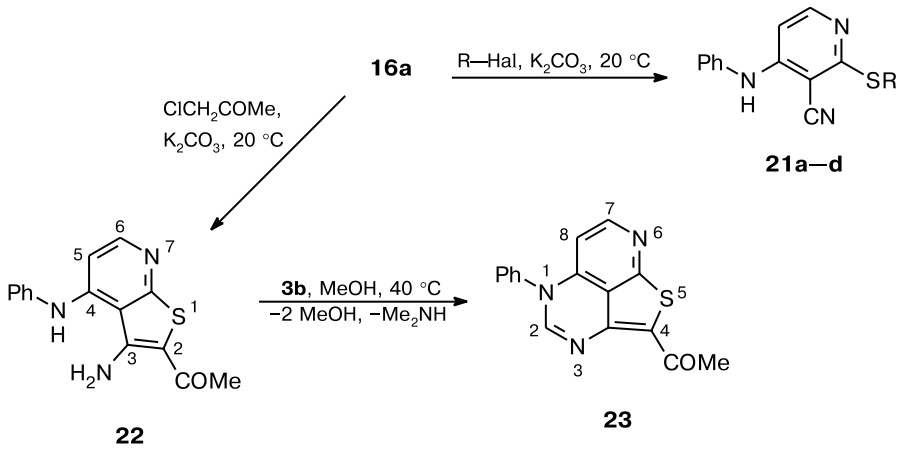


Therefore, the chemical behavior of enaminoamides **1** in the reaction with DMF acetal differs from that of enaminothioamide **14**. Dimethylformamide acetal reacts with **1** to give amidine **10**, which can be transformed into formylpyridone **11** under conditions of acid hydrolysis. By contrast, enaminothioamide **14** is alkylated with DMF acetal at the S atom, which excludes the formation of the formyl group upon the pyridine-ring closure. The replacement of the O atom with the S atom in pyrimidinones has no effect on hydrolysis of these compounds. In all cases, the reactions afford pyridine derivatives.

Scheme 10



Scheme 11



R = Et (**a**), Me (**b**), CH_2COOEt (**c**), CH_2CN (**d**)

The synthesis of pyridinethiones containing the thioxo and cyano groups in the *ortho* position opened up possibilities of performing heterocyclizations involving these groups. Alkylation of pyridinethione **16a** with haloalkanes in aqueous isopropyl alcohol in the presence of K_2CO_3 at 20 °C afforded the corresponding *S*-alkylated derivatives **21a—d**. Under the same conditions, compound **16a** was involved in the Thorpe—Ziegler reaction with chloroacetone,[8] which proceeded smoothly to give 1-acetyl-3-amino-4-anilinothieno[2,3-*b*]pyridine (**22**). Heating of thienopyridine **22** with acetal **3b** in methanol resulted in the pyrimidine-ring closure to give tricyclic compound **23** (the synthesis of another representative of this heterocyclic system has been described earlier[9]).

Experimental

The IR spectra were recorded on a Perkin—Elmer 457 instrument in Nujol mulls. The mass spectra (EI) were obtained on a Finnigan SSQ-710 mass spectrometer with direct inlet of the sample into the ion source. The ^{1}H NMR spectra were measured on a Bruker AC-200 spectrometer in DMSO-d_6. Two-dimensional HMBC NMR spectra were recorded on a Bruker DRX-500 instrument using the standard software. The course of the reactions and the purity of the compounds synthesized were monitored by TLC on Silufol UV-254 plates (ethyl acetate was used as the eluent, unless otherwise indicated; visualization with UV light). The melting points were determined on an Electrothermal 9100 instrument (UK) and are given in Table 1. The spectroscopic data for the compounds synthesized are given in

Table 1. Melting points and results of elemental analysis for compounds **7b**, **11**, **12**, **13a**,**b**, **14**, **15a**,**b**, **16a**,**b**, **19**, **20**, **21a—d**, **22**, and **23**

Compound	M.p./°C (solvent)	Found / Calculated (%)					Molecular formula
		C	H	N	S	Cl	
7b	304—306	66.32	4.34	16.32	–	–	$C_{14}H_{11}N_3O_2$
	(DMF)	66.40	4.37	16.59			
11	254—256	56.70	4.76	21.85	–	–	$C_9H_9N_3O_2$
	(Pr^iOH—DMF)	56.54	4.74	21.98			
12	272—274	–	–	16.19	–	14.00	$C_{14}H_8ClN_3$
	(DMF)	66.28	3.18	16.56		13.47	
13a	254—256	63.75	4.97	19.48	11.20	–	$C_{15}H_{14}N_4S$
	($PhCH_3$)	63.81	5.00	19.84	11.36		
13b	258—260	56.71	4.14	17.52	10.08	11.20	$C_{15}H_{13}ClN_4S$
	($PhCH_3$)	56.87	4.13	17.69	10.12	11.19	
14	172—174	50.12	6.68	25.02	18.91	–	$C_7H_{11}N_3S$
	(Pr^iOH)	49.68	6.55	24.83	18.94		
15a	171—172	60.86	5.18	19.35	15.07	–	$C_{11}H_{11}N_3S$
	(Pr^iOH)	60.80	5.10	19.34	14.76		
15b	192—193	52.30	3.90	16.91	12.70	14.09	$C_{11}H_{10}ClN_3S$
	(Pr^iOH)	52.48	4.00	16.69	12.74	14.08	
16a	284—288	63.26	3.96	18.64	14.17	–	$C_{12}H_9N_3S$
	(BuOH)	63.41	3.99	18.49	14.11		
16b	267—271	55.67	3.13	15.99	12.20	14.00	$C_{12}H_8ClN_3S$
	(BuOH)	55.07	3.08	16.05	12.25	13.55	
19	119	55.77	5.70	21.74	16.60	–	$C_9H_{11}N_3S$
	(hexane)	55.93	5.74	21.74	16.59		
20	112—113	63.26	4.64	14.64	11.32	–	$C_{15}H_{13}N_3OS$
	(hexane)	63.58	4.62	14.83	11.32		
21a	124—125	65.62	5.05	16.47	12.49	–	$C_{14}H_{13}N_3S$
	(Pr^iOH)	65.85	5.13	16.46	12.56		
21b	127—127.5	64.73	4.55	17.53	13.40	–	$C_{13}H_{11}N_3S$
	(Pr^iOH)	64.71	4.59	17.41	13.29		
21c	256—257	63.01	3.81	21.21	12.03	–	$C_{14}H_{10}N_4S$
	(Pr^iOH)	63.14	3.78	21.04	12.04		
21d	113—114	61.54	4.84	13.31	10.19	–	$C_{16}H_{15}N_3O_2S$
	(Pr^iOH)	61.32	4.82	13.41	10.23		
22	135	63.67	4.85	14.82	11.47	–	$C_{15}H_{13}N_3OS$
	(Pr^iOH)	63.58	4.62	14.83	11.32		
23	284—287	65.76	3.88	14.15	10.89	–	$C_{16}H_{11}N_3OS$
	(BuOH)	65.51	3.78	14.32	10.93		

Table 2. ^{1}H NMR spectra of compounds **4b** and **13a,b**

Compound	δ (*J*/Hz)			
	H(2) (s, 1 H)	H(1′), H(2′) (both d, 1 H each)	NMe_2 (br.s, 6 H)	Ar
4b	8.15	4.08, 7.85 ($^3J_{H,H}$ = 12.9)	2.55, 3.00	2.39 (s, 3 H, Me); 7.38 (m, 4 H, C_6H_4)
13a	8.08	4.20, 7.86 ($^3J_{H,H}$ = 12.8)	2.65, 2.94	7.62 (m, 5 H, Ph)
13b	8.12	4.17, 8.05 ($^3J_{H,H}$ = 12.8)	2.68, 3.13	7.69 (m, 4 H, C_6H_4)

Tables 2 and 3. Cyanothioacetamide was prepared according to a known procedure.[10] Compound **14** was synthesized with the use of *N,N*-dimethylacetamide dimethyl acetal (90%, Lancaster, 1642).

5-Cyano-6-(2-dimethylaminovinyl)-4-oxo-1-phenyl-1,4-dihydropyrimidine (4a). A mixture of enaminoamide **2a** (2.00 g, 9.9 mmol) and acetal **3b** (21.8 mmol) in dry toluene (10 mL) was refluxed for 13 h, kept at ~10 °C for ~14 h, and ground. The precipitate that formed was filtered off, washed with toluene, and dried. Compound **4a** was obtained in a yield of 2.18 g (82%), m.p. 233—236 °C (*cf.* lit. data[1]: m.p. 235—236 °C, from EtOH).

5-Cyano-6-(2-dimethylaminovinyl)-1-(4-methylphenyl)-4-oxo-1,4-dihydropyrimidine (4b) was synthesized analogously to compound **4a**. The yield was 93%, m.p. 266—268 °C (*cf.* lit. data[2]: m.p. 264—266 °C, from EtOH). MS, *m/z* (I_{rel} (%)): 280 $[M]^+$ (100), 236 $[M - NMe_2]^+$ (24), 210 $[M - NMe_2 - CN]^+$ (27), 187 (22), 119 (73), 91 $[C_6H_4 - Me]^+$ (51).

***N*-(Dimethylaminomethylene)-2-cyano-5-dimethylamino-3-phenylamino-2,4-pentadieneamide (5a).** A mixture of compound **2a** (28.65 g, 0.14 mol) and acetal **3a** or **3b** (0.35 mol) in anhydrous EtOH (200 mL) was refluxed for 6 h. The solution was cooled and kept for ~14 h. The resulting mixture was ground. The precipitate that formed was filtered off, washed with anhydrous EtOH, and dried. The precipitate was obtained in a yield of 32.8 g, m.p. 160—170 °C. According to the ^{1}H NMR spectroscopic data, the mixture contained compounds **4a** and **5a** in a ratio of 1 : 8.

Compound **5a**. ^{1}H NMR, δ: 2.80 (br.s, 6 H, NMe_2); 2.98 and 3.10 (both s, 3 H each, NMe_2); 4.77 (d, 1 H, H(4), $^3J_{H,H}$ = 13.1 Hz); 7.16 (t, 1 H, *p*-Ph), $^3J_{H,H}$ = 7.6 Hz); 7.22 (d, 2 H, *o*-Ph, $^3J_{H,H}$ = 7.6 Hz); 7.35 (t, 2 H, *m*-Ph, $^3J_{H,H}$ = 7.6 Hz); 7.36 (d, 1 H, H(5), $^3J_{H,H}$ = 13.2 Hz); 8.38 (br.s, 1 H, amidine CH); 12.43 (br.s, 1 H, NH). Analogously, refluxing in toluene for 3 h afforded a mixture of *N*-(dimethylaminomethylene)-2-cyano-5-dimethylamino-3-(4-methylphenylamino)-2,4-pentadieneamide (**5b**) and pyrimidinone **4b** in a ratio of ~1 : 1.

Compound **5b**. ^{1}H NMR, δ: 2.32 (s, 3 H, C_6H_4Me); 2.80 (br.s, 6 H, NMe_2); 2.99 and 3.11 (both s, 3 H each, NMe_2); 4.70 (d, 1 H, H(4), $^3J_{H,H}$ = 13.2 Hz); 7.10 (m, 4 H, C_6H_4); 7.35 (d, 1 H, H(5), $^3J_{H,H}$ = 13.2 Hz), 8.35 (br.s, 1 H, amidine CH), 12.44 (br.s, 1 H, NH).

3-Cyano-5-formyl-2-oxo-4-phenyl-1,2-dihydropyridine (7a). A 90% aqueous AcOH solution (10 mL) was added to a mixture of compounds **4a** and **5a** (1.0 g), which was prepared according to the above-described procedure and contained 90 wt. % of **5a** (0.90 g, 2.9 mmol). The reaction mixture was stirred at 20 °C for 20 h. The precipitate that formed was filtered off, washed with water, and dried. Formylpyridine **7a** was obtained in a yield of 0.51 g (74% with respect to **5a**).

3-Cyano-5-formyl-4-(4-methylphenyl)-2-oxo-1,2-dihydropyridine (7b) was synthesized analogously to formylpyridine **7a**. The yield was 61%. ^{1}H NMR, δ: 2.37 (s, 3 H, Me); 7.25 (br.s, 4 H, C_6H_4); 8.42 (s, 1 H, H(6)); 9.63 (s, 1 H, CHO); 10.56 (br.s, 1 H, NH). IR, ν/cm^{-1}: 2217 (CN), 1660 (CHO), 1627. MS, *m/z* (I_{rel} (%)): 253 $[M]^+$ (100), 224 $[M - CHO]^+$ (54), 198 $[M - CHO - CN]^+$, 161 $[M - PhMe]^+$ (20), 91 $[C_6H_4 - CH_3]^+$ (51).

2-Cyano-3,5-bis(dimethylamino)-1-(dimethylaminomethylene)-2,4-pentadieneamide (10). A mixture of enaminoamide **1** (0.76 g, 4.97 mmol) and 60% acetal **3b** (4.0 mL) in dry toluene (6 mL) was refluxed for 13 h. The reaction mixture was concentrated *in vacuo* and the resulting oil was triturated in light petroleum (b.p. 50—70 °C). The precipitate that formed was filtered off, washed with light petroleum, and dried. Compound **10** was obtained in a yield of 1.27 g (98%) as yellow crystals, m.p. 128—133 °C. ^{1}H NMR, δ: 2.96, 3.04, and 3.06 (all br.s, 18 H, 3 NMe_2); 4.75 (d, 1 H, H(4), $^3J_{H,H}$ = 12.2 Hz); 7.39 (d, 1 H, H(5), $^3J_{H,H}$ = 12.2 Hz); 8.23 (br.s, 1 H, amidine CH). MS, *m/z* (I_{rel} (%)): 263 $[M]^+$ (37), 219 $[M - NMe_2]^+$ (63), 192 $[M - NMe_2 - HCN]^+$ (43), 165 $[M - NMe_2 - 2HCN]^+$ (20), 147 (49), 121 (59), 99 (100).

3-Cyano-5-formyl-4-dimethylamino-2-oxo-1,2-dihydropyridine (11). Compound **10** (100 mg, 0.38 mmol) was added to 90% aqueous AcOH (1.0 mL). The reaction solution was kept at 20 °C for 4 days. Then the reaction mixture was ground. The precipitate that formed was filtered off, washed with ethyl acetate, and dried. Compound **11** was obtained in a yield of 50 mg (71%). ^{1}H NMR, δ: 3.14 (s, 6 H, NMe_2); 8.14 (s, 1 H, H(6)); 9.49 (br.s, 1 H, CHO); 12.18 (br.s, NH). MS, *m/z* (I_{rel} (%)): 191 $[M]^+$ (69), 174 $[M - OH]^+$ (41), 148 $[M - HNCO]^+$ (34), 134 $[M - CO - CHO]^+$ (45), 44 $[NMe_2]^+$ (100).

3-Chloro-4-cyano-8-methylbenzo[*b*][1,6]naphthyridine (12). A mixture of compound **7b** (0.14 g, 2 mmol) and $Et_3N \cdot HCl$ (0.11 g, 1.5 mmol) in $POCl_3$ (1.5 mL) was refluxed with stirring for 1 h. Then the reaction mixture was cooled. The precipitate that formed was filtered off, treated with an excess of water, filtered once again, washed with water, and dried. Compound **12** was obtained in a yield of 0.07 g (50%) as yellow crystals. ^{1}H NMR, δ: 2.60 (s, 3 H, Me); 7.99 (q, 1 H, H(7), $^3J_{H(7),H(6)}$ = 8.0 Hz, $J_{H(7),H(9)}$ = 1.5 Hz); 8.08 (br.s, 1 H, H(9)); 8.16 (d, 1 H, H(6), $^3J_{H,H}$ = 8.0 Hz); 9.45 (s, 1 H, H(10)); 9.73 (s, 1 H, H(1)). MS, *m/z* (I_{rel} (%)): 253 $[M]^+$ (100), 216 (10).

5-Cyano-6-(2-dimethylaminovinyl)-1-phenyl-4-thioxo-1,4-dihydropyrimidine (13a). A 2.2-fold excess of acetal **3b** was added to a solution of compound **15a** (15.00 g, 88.7 mmol) in dry toluene (160 mL) under argon. The reaction mixture was refluxed with stirring for 13 h, argon being passed through the reaction medium. Then the reaction mixture was cooled to

~10 °C, kept for ~14 h, and ground. The precipitate that formed was filtered off, washed with hexane and diethyl ether, and dried. Compound **13a** was obtained in a yield of 9.70 g (39%) as yellow crystals. The course of the reaction and the purity of product **13a** was monitored by TLC ($CHCl_3$—MeOH, 10 : 1, as the eluent). MS, *m/z* (I_{rel} (%)): 282 $[M]^+$ (100), 238 $[M - NMe_2]^+$ (51).

1-(4-Chlorophenyl)-5-cyano-6-(2-dimethylaminovinyl)-4-thioxo-1,4-dihydropyrimidine (13b) was synthesized from compound **15b** analogously to **13a**. Yellow crystals, the yield was 50%. MS, *m/z* (I_{rel} (%)): 316 $[M]^+$ (100), 301 $[M - Me]^+$ (52), 272 $[M - NMe_2]^+$ (43).

2-Cyano-3-dimethylaminothiocrotonamide (14). A 90% *N,N*-dimethylacetamide dimethyl acetal solution (0.81 g, 5.48 mmol) was added to a solution of cyanothioacetamide (0.50 g, 5 mmol) in dry MeOH (4 mL) under argon. The reaction mixture was stirred at 10 °C for 2 h and kept for ~14 h. The precipitate that formed was filtered off, washed with Pr^iOH, and dried. Compound **14** was obtained in a yield of 0.42 g (50%) as dingy-yellow crystals. IR, ν/cm^{-1}: 3356, 3266, 3133 (NH_2), 2183 (CN). MS, *m/z* (I_{rel} (%)): 169 $[M]^+$ (22), 135 $[M - H_2S]$ (100).

3-Anilino-2-cyanothiocrotonamide (15a). Glacial AcOH (75 mL) and aniline (9.57 mL, 107 mmol) were added to compound **14** (14.79 g, 87.5 mmol) under argon. The reaction mixture was refluxed with stirring for 5 h, argon being passed through the reaction medium. The resulting solution was cooled and kept for 12 h. The precipitate that formed was filtered off, washed with water and diethyl ether, and dried. Compound **15a** was obtained in a yield of 15.84 g (83%) as colorless crystals. ^{1}H NMR, δ: 2.32 (s, 3 H, Me); 7.24—7.49 (m, 5 H, Ph); 7.81 and 8.79 (both br.s, 1 H each, $CSNH_2$); 14.45 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3352, 3285, 3186 (NH, NH_2), 2190 (CN). MS, *m/z* (I_{rel} (%)): 217 $[M]^+$ (96), 200 $[M - NH_3]^+$ (19), 183 $[M - H_2S]^+$ (100), 157 $[M - HS - HCN]^+$ (70).

3-(4-Chlorophenylamino)-2-cyanothiocrotonamide (15b) was synthesized analogously to thioamide **15a** as white crystals in 84% yield. ^{1}H NMR, δ: 2.31 (s, 3 H, Me); 7.30—7.46 (both d, 2 H each, C_6H_4, $^3J_{H,H}$ = 8.0 Hz); 7.48 and 8.80 (both br.s, 1 H each, $CSNH_2$); 14.43 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3341, 3288, 3189 (NH, NH_2), 2195 (CN). MS, *m/z* (I_{rel} (%)): 251 $[M]^+$ (100), 218 $[M - SH]^+$ (98), 183 $[M - SH - Cl]^+$ (24).

4-Anilino-3-cyano-2-thioxo-1,2-dihydropyridine (16a).
A. A 1 *M* aqueous KOH solution (80 mL) was added to pyrimidinethione **13a** (4 g, 14.18 mmol) and the mixture was refluxed with stirring for 2.5 h. The resulting solution was cooled and acidified with AcOH to pH 6. The precipitate that formed was filtered off, washed with water and diethyl ether, and dried. Product **16a** was obtained in a yield of 2.56 g (79%) as a white powder. MS, *m/z* (I_{rel} (%)): 227 $[M]^+$ (74), 226 $[M - H]^+$ (100), 194 $[M - SH]^+$ (9), 167 $[M - SH - HCN]^+$ (11).

B. A solution of pyrimidinethione **13a** (0.30 g, 1.06 mmol) in 50% aqueous AcOH (4 mL) was kept at 20 °C for 4 days. The precipitate that formed was filtered off, washed with diethyl ether, and dried. Compound **16a** was obtained in a yield of 0.14 g (58%).

C. A suspension of pyrimidinethione **13a** (150 mg, 0.532 mmol) in distilled water (5 mL) was refluxed with stirring for 2 h. The reaction mixture was cooled. The precipitate that formed was filtered off, washed with water, and dried. Compound **16a** was obtained in a yield of 100 mg (83%).

D. A mixture of pyrimidinethione **13a** (0.3 g, 1.06 mmol) and aniline (0.2 mL) in Pr^iOH (6 mL) was refluxed with stirring for 4 h. The alcohol was removed *in vacuo* and the residue was triturated with water. The precipitate that formed was filtered off, washed with water, and dried. Compound **16a** was obtained in a yield of 0.14 g (58%).

4-(4-Chlorophenyl)amino-3-cyano-2-thioxo-1,2-dihydropyridine (16b) was synthesized from compound **13b** analogously to thione **16a** (method *A*) as white crystals in 55% yield. MS,

Table 3. ^{1}H NMR spectra of compounds **16a,b**, **19**, **20**, and **21a,b***

Compound	δ (*J*/Hz)		
	H(5), H(6)	S—R	N(4)R^1, R^2
16a	6.16 (H(5)); 7.42 (H(6), $^3J_{H,H}$ = 7.4)	–	9.27 (br.s, 1 H, NH); 7.25—7.44 (m, 5 H, Ph)
16b**	6.18 (H(5)**, $^3J_{H,H}$ = 7.4)	–	9.37 (br.s, 1 H, NH); 7.29—7.51 (m, 5 H, *p*-ClC_6H_4 and H(6))
19	6.30, 8.05, ($^3J_{H,H}$ = 6.4)	2.54 (s, 3 H, SMe, $^1J_{C,H}$ = 141.7)	3.19 (s, 6 H, NMe_2, $^1J_{C,H}$ = 138.0)
20	7.16, 8.73 ($^3J_{H,H}$ = 5.3)	1.34 (t, 2 H, CH_2); 3.28 (q, 3 H, Me, $^3J_{H,H}$ = 7.4)	8.78 (s, 1 H, CHO); 7.30 (d, 2 H, H(2′), H(6′)); 7.41 (m, 1 H, H(4′)); 7.49 (t, 2 H, H(3′), H(5′), $^3J_{H,H}$ = 8.0)
21a	6.59, 8.12 ($^3J_{H,H}$ = 6.1)	1.31 (t, 2 H, CH_2); 3.20 (q, 3 H, Me, $^3J_{H,H}$ = 7.3)	8.97 (br.s, 1 H, NH); 7.21—7.45 (m, 5 H, Ph)
21b	6.61, 8.14 ($^3J_{H,H}$ = 6.1)	2.55 (s, 1 H, Me)	9.07 (br.s, 1 H, NH); 7.21—7.41 (m, 5 H, Ph)

* The spectra were recorded in $CDCl_3$.
** The signal for H(6) overlaps with a multiplet of the aryl group.

m/z (I_{rel} (%)): 262 $[M + H]^+$ (77), 260 $[M - H]^+$ (100), 225 $[M - HCl]^+$ (20).

3-Cyano-4-dimethylamino-2-methylthiopyridine (19). A mixture of enamine **14** (0.8 g, 4.73 mmol) and acetal **3b** (12.31 mmol) in dry toluene (5 mL) was refluxed with stirring for 14 h, argon being passed through the reaction medium. The reaction mixture was concentrated *in vacuo*, 90% aqueous AcOH (10 mL) was added to the oily residue, the mixture was kept for 24 h, and water (20 mL) was added. The black solid precipitate that formed was filtered off, washed with water, dried, and extracted with hexane. Compound **19** was obtained in a yield of 0.45 g (46%). MS, *m/z* (I_{rel} (%)): 193 $[M]^+$ (100), 178 $[M - Me]^+$ (28), 165 (22), 132 $[M - SMe - CH_2]^+$ (30).

3-Cyano-2-ethylthio-4-formylanilinopyridine (20). Boron trifluoride etherate (0.50 mL) was added with stirring and cooling to 0—5 °C to a solution of triethyl orthoformate (0.51 mL) in CH_2Cl_2 (3 mL). Then a solution of compound **13a** (0.3 g, 1.06 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was refluxed with stirring for 2 h and concentrated *in vacuo* at 20 °C. The resulting oil was triturated successively in hexane (2×10 mL) and a concentrated Na_2CO_3 solution (~15 mL) and kept for 2 days. The precipitate that formed was filtered off, washed with water and diethyl ether, and dried. Technical product **20** containing ~10% of compound **21a** was obtained in a yield of 0.20 g. After crystallization from hexane, analytically pure compound **20** was obtained in a yield of 0.12 g as white crystals. ^{13}C NMR (DMSO-d_6), δ: 14.6, 24.8 (Et); 105.7 (C(3)); 113.9 (CN); 119.0 (C(5)); 124.9, 128.3, 130.4 (Ph); 139.6 (C(1′)); 150.8 (C(4)); 154.3 (C(6)); 162.3 (CHO); 164.5 (C(2)). The assignment of the signals in the ^{13}C NMR spectrum was made based on HMBS and HSQC experiments. The characteristic correlation peaks in the HMBS spectrum are as follows: $C(2)/CH_2$ = 164.5/3.26 ppm, C(4)/CHO = 150.8/8.78 ppm. IR, ν/cm^{-1}: 1691, 1700 (CO), 2227 (CN). MS, *m/z* (I_{rel} (%)): 283 $[M]^+$ (46), 255 $[M - CO]^+$ (80), 254 $[M - CHO]^+$ (93), 226 $[M - CO - Et]^+$ (100), 194 $[M - CO - SEt]^+$ (41).

2-Alkylthio-4-anilino-3-cyanopyridines (21a—d) (general procedure). The corresponding alkylating agent (1.60 mmol) was added to a mixture of pyridinethione **16a** (0.30 g, 1.32 mmol), K_2CO_3 (0.3 g), Pr^iOH (6 mL), and water (2 mL). The reaction mixture was stirred at 20 °C for 24 h. Then water (10—15 mL) was added and the mixture was stirred. The precipitate that formed was filtered off, thoroughly washed with water and hexane, and dried. Compounds **21a—d** were obtained as white crystals.

4-Anilino-3-cyano-2-ethylthiopyridine (21a). ^{13}C NMR (DMSO-d_6), δ: 14.8, 23.9 (Et); 91.3 (C(3)); 104.7 (C(5)); 115.1 (CN); 123.7, 125.4, 129.6 (Ph); 138.7 (C(1′)); 151.3 (C(6)); 154.1 (C(4)); 163.6 (C(2)). The assignment of the signals in the ^{13}C NMR spectrum was made based on Dept experiments.

Compound **21a** was also synthesized independently. A mixture of compound **20** (0.10 g) and piperidine (0.10 g) in MeOH (2.5 mL) was refluxed with stirring for 3.5 h. After cooling, water (10 mL) was added. The precipitate that formed was filtered off, washed with water and diethyl ether, and dried. Compound **21a** was obtained in a yield of 0.09 g (100%).

4-Anilino-3-cyano-2-methylthiopyridine (21b) was synthesized according to the general procedure. The yield was 87%. MS, *m/z* (I_{rel} (%)): 241 $[M]^+$ (100), 194 $[M - SMe]^+$ (54).

4-Anilino-3-cyano-2-ethoxycarbonylmethylthiopyridine (21c) was synthesized according to the general procedure. The yield was 85%. MS, *m/z* (I_{rel} (%)): 313 $[M]^+$ (61), 267 $[M - SCH_2]^+$ (50), 240 $[M - COOEt]^+$ (100).

4-Anilino-2-cyanomethylthio-3-cyanopyridine (21d) was synthesized according to the general procedure. The yield was 91%. MS, *m/z* (I_{rel} (%)): 266 $[M]^+$ (100), 194 $[M - SCH_2CN]^+$ (29).

1-Acetyl-3-amino-4-anilinothieno[2,3-*b*]pyridine (22). Chloroacetone (0.20 mL) was added to a solution of compound **16a** (0.3 g, 1.32 mmol) and K_2CO_3 (0.2 g) in 75% aqueous Pr^iOH (8 mL). The reaction mixture was stirred at 20 °C for 20 h and then water (10 mL) was added. The precipitate that formed was filtered off, washed with diethyl ether, and dried. Compound **22** was obtained in a yield of 0.34 g (91%). ^1H NMR, δ: 2.21 (s, 3 H, Me); 6.64 (d, 1 H, H(5), $^3J_{H,H}$ = 5.6 Hz); 7.00—7.70 (m, 5 H, Ph); 7.76 (br.s, 2 H, NH_2); 8.10 (d, 1 H, H(6), $^3J_{H,H}$ = 5.6 Hz); 8.37 (br.s, 1 H, NH). IR, ν/cm^{-1}: 3360, 3289, 3156 (NH, NH_2); 1604 (CO). MS, *m/z* (I_{rel} (%)): 283 $[M]^+$ (66), 268 $[M - Me]^+$ (100), 240 $[M - COMe]^+$ (41).

4-Acetyl-1-phenyl-5-thia-1,3,6-triazaacenaphthene (23). Acetal **3b** (1.15 mmol) was added to a solution of compound **22** (0.25 g, 0.882 mmol) in MeOH (5 mL) at 40 °C for 6 h. The precipitate that formed was filtered off, washed with hexane, and dried. Compound **23** was obtained in a yield of 0.22 g (85%). ^1H NMR, δ: 2.67 (s, 3 H, Me); 6.24 (d, 1 H, H(8), $^3J_{H,H}$ = 6.0 Hz); 7.55—7.65 (m, 5 H, Ph); 7.97 (br.s, 1 H, H(2)); 8.27 (d, 1 H, H(7), $^3J_{H,H}$ = 6.0 Hz). IR, ν/cm^{-1}: 1627 (CO). MS, *m/z* (I_{rel} (%)): 293 $[M]^+$ (90), 278 $[M - Me]^+$ (100), 250 $[M - COMe]^+$ (46).

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