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SYNTHESIS AND CHEMICAL CONVERSIONS OF 2-CHLORO-3-CYANO-4-METHYLAMINO-5-NITROPYRIDINE

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5-Cyano-6-(β-dimethylamino)vinyl-1-methyl-4-pyrimidinone was synthesized by the interaction of α-cyano-β-(N-methylamino)crotonamide with N,N-dimethylformamide diethylacetal. Recyclization of the product in alkaline medium leads to 3-cyano-4-methylamino-2-pyridone. Nitration of the latter and transformation of the nitropyridone by boiling in $POCl_3$ gave 2-chloro-3-cyano-4-methylamino-5-nitropyridine. This is a key compound for various transformations including the synthesis of derivatives of dipyrido[1,2-a:3,2-e]pyrimidine, thieno[2,3-b]pyridine, and (2-pyridylamino)polyene derivatives.

Keywords: nitropyridine, 2-pyridone, 4-pyrimidinone, Torp–Ziegler reaction

Previously we developed a general approach to the synthesis of derivatives of 4-amino-3-cyano-2-pyridone based on the cyclization of enamino amides under the action of amideacetals into derivatives of 4-pyrimidone and recyclization of the latter in alkaline media [1-3]. Recently it was established on investigating the properties and conversions of 2-chloro-3-cyano-5-nitropyridine that this compound reacts smoothly with pyridine with the formation of a pyridylpyridinium salt, which is a promising starting material for the synthesis of various pyridine derivatives, including condensed pyridines [4].

The aim of the present work was to combine these two approaches, to synthesize derivatives of 3-cyano-5-nitro-2-pyridone containing an additional electron-donating functional substituent (substituted amino group) at position 4 of the pyridine ring, and to study the transformations of a key compound, 2-chloro-3-cyano-4-methylamino-5-nitropyridine (**1**), into various pyridine derivatives. In the first stage of the investigation the possibility was studied of synthesizing 3-cyano-4-isopropylamino-2-pyridone (**2**), starting from α-cyano-β-isopropylaminocrotonamide (**4**), itself obtained by the transamination of the tertiary enamino amide **3** [5] with isopropylamine. Interaction of compound **4** with DMF diethylacetal (**5**) occurs smoothly, but in this case introduction of the β-dimethylaminovinyl fragment into position 6 of the 4-pyrimidinone ring was unsuccessful. Probably steric difficulties arising from the presence of the bulky isopropyl group in position 1 impede attack of acetal **5** at the 6-CH_3 group. Condensation of acetal under the usual and under more forcing conditions does not occur. As a result 5-cyano-1-isopropyl-6-methyl-1,4-dihydro-4-pyrimidinone (**6**) is formed which is incapable of recyclizing into the desired pyridone **2** (Scheme 1).

As a consequence of this the previously described amide of α-cyano-β-(N-methylamino)crotonic acid (**7**) [6] was selected for subsequent work. Compound **7** was transformed into 3-cyano-4-methylamino-2-pyridone (**10**) through 5-cyano-1,6-dimethyl-1,4-dihydro-4-pyrimidinone (**8**) and 5-cyano-6-(N,N-dimethylaminovinyl)-1-methyl-1,4-dihydro-4-pyrimidinone (**9**) by the usual method. Compound **10** was

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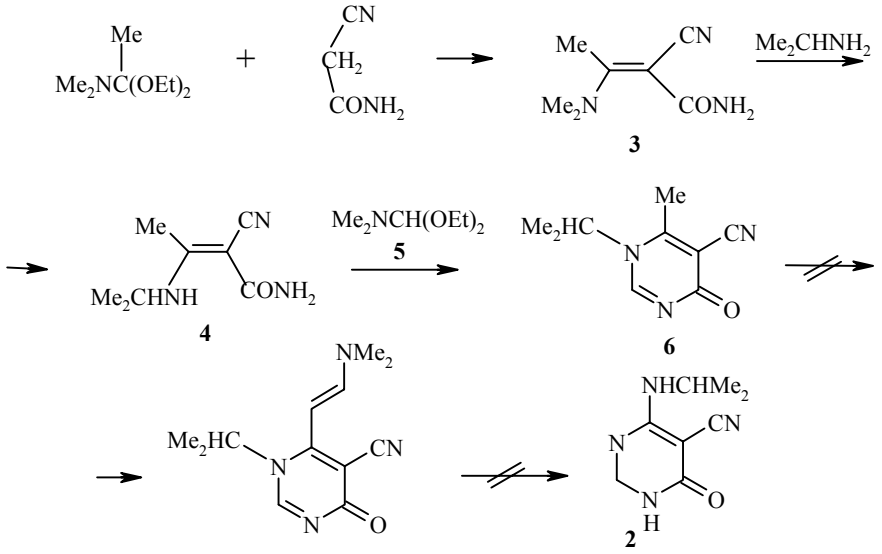
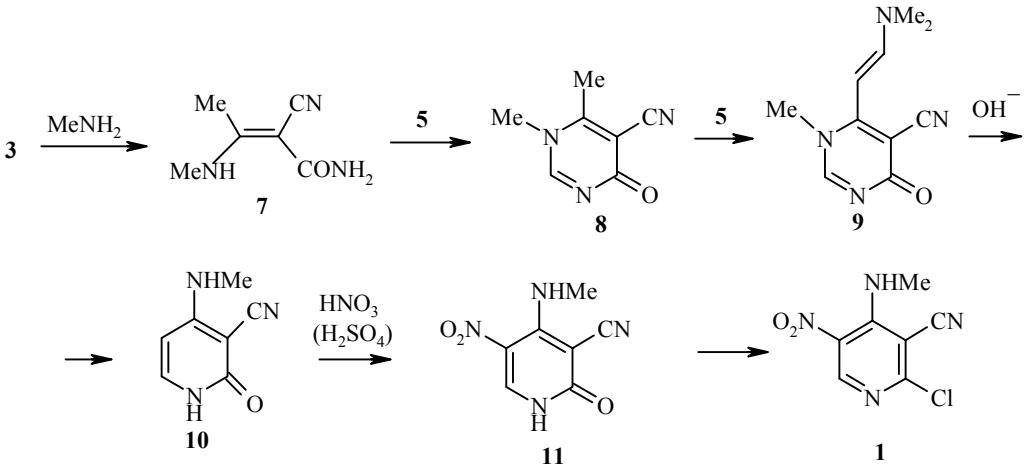
Scheme 1



subjected to nitration at position 5 and the nitro derivative **11** obtained was converted by boiling in phosphorus oxychloride into 2-chloro-3-cyano-4-methylamino-5-nitropyridine (**1**), which is the main key intermediate for the subsequent syntheses.



It turned out that in compound **1**, in spite of the presence at position 4 of a strong electron-donating substituent, the chlorine atom at position 2 was fairly reactive and may easily be replaced by various groups under nucleophilic attack. The interaction of chloropyridine **1** with 2-aminopyridine takes place in the same direction as for 2-chloro-3-cyano-5-nitropyridine [4], with the formation of 5-imino-4-methylamino-3-nitrodipyrido-[1,2-*a*:3,2-*c*]pyrimidine (**12**).

The reaction of compound **1** with pyridine also proceeds extremely smoothly. In this case the pyridyl-2-pyridinium salt **13** is formed, which according to the previously well-founded scheme of [4] reacts with piperidine with the formation of the 2-amino derivative **14**, giving with alkali the pyridylaminodiene **15,** and with malono-dinitrile the pyridylaminotriene **16**. The ability of the pyridinium fragment to be replaced on interaction with nucleophilic reagents is also confirmed by the reaction of salt **13** with thioglycolic ester with the formation of 3-cyano-2-ethoxycarbonylmethylthio-4-methylamino-5-nitropyridine (**17**). Under the action of

sodium ethylate the latter smoothly undergoes Torp–Ziegler cyclization [7] with the formation of 3-amino-2-ethoxycarbonyl-4-methylamino-5-nitrothieno[2,3-*b*]pyrimidine (**18**). Signals were observed in the ^{1}H NMR spectrum of compound **12** in DMSO-d_6 at 2.94 (3H, s, NH$\underline{CH_3}$); 7.22-9.39 (4H, m, arom. H); 8.66 (1H, s, 2-H); 8.81 ppm (1H, br. s, NH); in the spectrum of compound **15** at 3.30 (3H, d, NH$\underline{CH_3}$); 6.04 (1H, q, J_1 = 8.6, J_2 = 14.7 Hz, δ-H); 6.55 (1H, q, J_1 = 11.3, J_2 = 13.2 Hz, β-H); 7.48 (1H, q, J_1 = 14.7, J_2 = 11.3 Hz, γ-H); 8.00 (1H, d, J = 13.2 Hz, α-H); 8.93 (1H, s, 6-H); 9.03 (1H, q, J = 6.4 Hz, $\underline{NH}CH_3$); 9.43 (1H, d, J = 8.6 Hz, CHO); 10.41 ppm (1H, br. s, 2-NH); in the spectrum of triene **16** at 3.30 (N$\underline{HCH_3}$ coinciding with the signal of water in DMSO-d_6); 6.58 (2H, m, β-, δ-H); 7.44 (1H, q, J_1 = 12, J_2 = 14 Hz, γ-H); 7.96 (1H, d, J = 12 Hz, ε-H); 8.14 (1H, d, J = 13.2 Hz, α-H); 8.95 (1H, s, 6-H); 9.06 (1H, q, J = 6 Hz, $\underline{NH}CH_3$); 10.56 ppm (1H, br. s, NH).

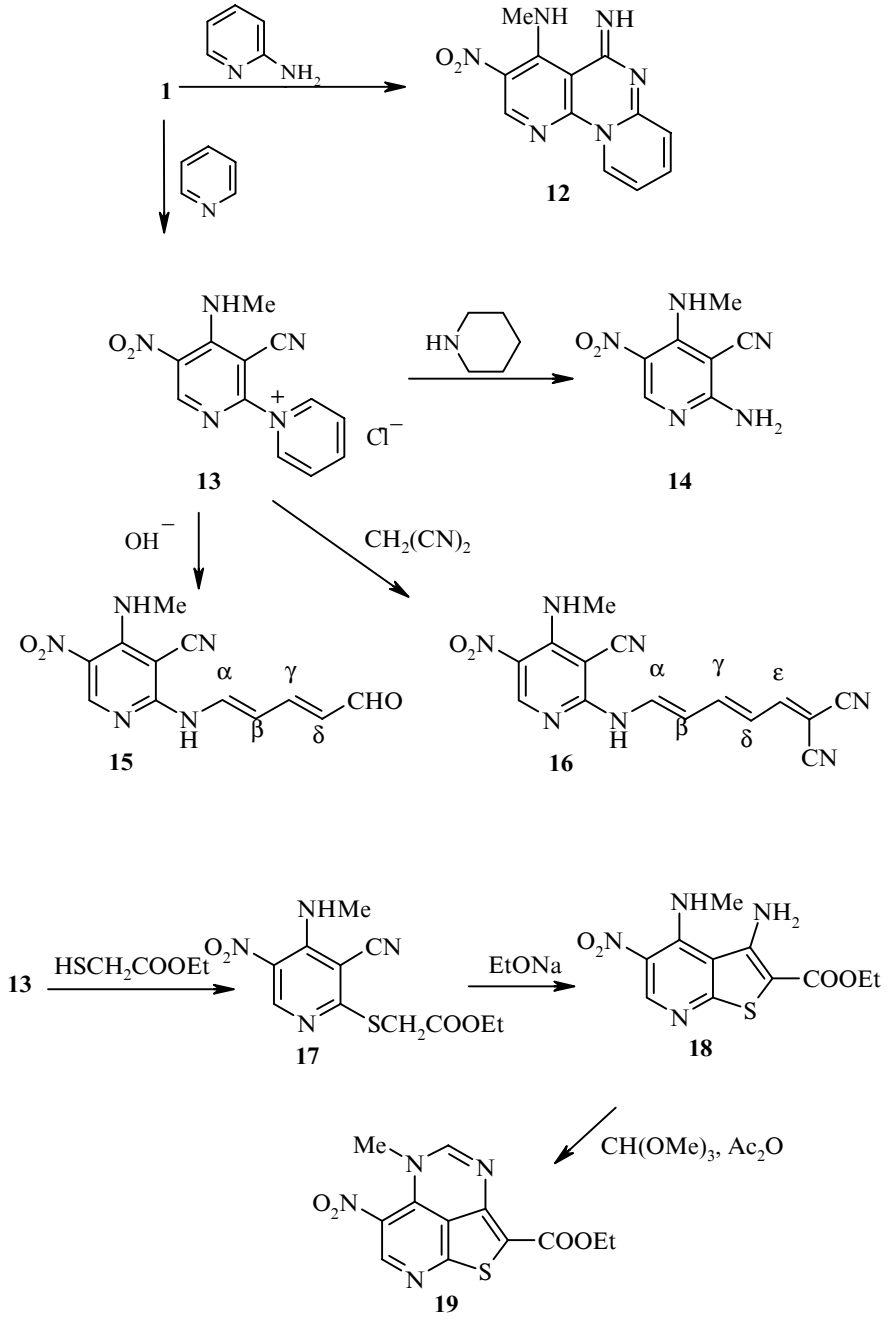


TABLE 1. Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp*, °C	Yield, %
		C	H	N		
1*[2]	$C_7H_5ClN_4O_2$	39.2 39.5	2.4 2.3	26.7 26.3	32-134	70
4	$C_8H_{13}N_3O$	57.5 57.5	8.0 7.8	25.1 25.1	166-167	87
6	$C_9H_{11}N_3O$	61.3 61.0	6.5 6.3	24.1 23.7	279-273	85
7	$C_6H_9N_3O$	52.0 51.8	6.4 6.5	30.0 30.2	199-200	95
8	$C_7H_7N_3O$	56.1 56.4	4.9 4.7	28.3 28.2	189-191	79
9	$C_{10}H_{12}N_4O$	59.1 58.8	6.0 5.4	28.0 27.4	232-234	76
10	$C_7H_7N_3O$	56.2 56.4	4.8 4.8	28.2 28.2	274-276	85
11	$C_7H_6N_4O_3$	43.2 43.3	3.3 3.3	28.8 28.9	302-305	41
12	$C_{12}H_{10}N_6O_2$	53.0 53.3	3.7 3.7	31.1 31.1	>360	84
13*[3]	$C_{12}H_{10}ClN_5O_2$	49.5 49.4	3.8 3.5	24.1 24.0	202-204	94
14	$C_7H_7N_5O_2$	43.8 43.5	3.7 3.7	36.3 36.9	320-322	72
15	$C_{12}H_{11}N_5O_3$	52.8 52.7	2.4 2.3	26.7 26.5	225-227	92
16	$C_{15}H_{11}N_7O_2$	56.1 56.1	3.4 3.5	30.5 30.5	>360	60
17*[4]	$C_{11}H_{12}N_4O_4S$	44.4 44.6	4.4 4.1	19.2 18.9	122-124	68
18*[5]	$C_{11}H_{12}N_4O_4S$	44.5 44.6	4.4 4.1	19.0 18.9	163-165	63
19	$C_{10}H_{12}N_6O_2$	48.7 48.4	4.9 4.9	34.1 33.9	238-240	84

* Solvents for crystallization: EtOH (compounds **1**, **7-10**, **13**, **15**, **17**), *i*-PrOH (**4**, **6**, **18**), AcOH (**11**), water–DMF (**14**), MeCN (**19**).

*[2] Found, %: Cl 16.9. Calculated, %: Cl 16.7.

*[3] Found, %: Cl 12.0. Calculated, %: Cl 12.2.

*[4] Found, %: S 10.9. Calculated, %: S 10.8.

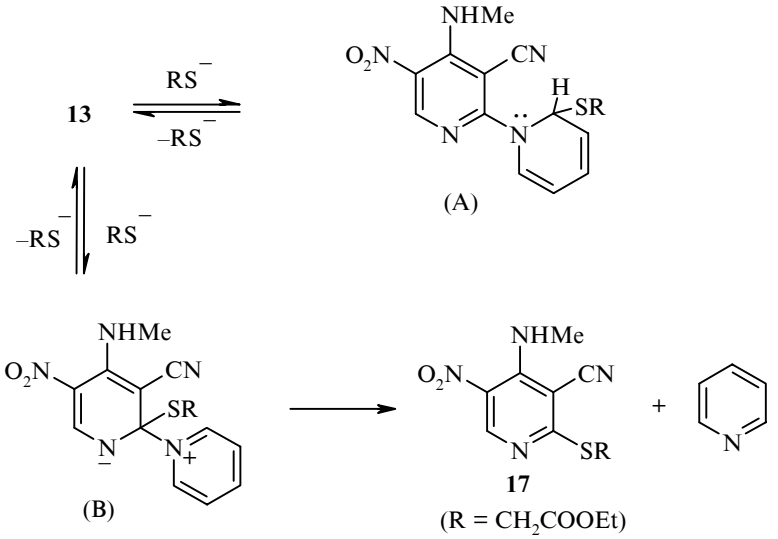
*[5] Found, %: S 11.2. Calculated, %: S 10.8

TABLE 2. ^{1}H NMR Spectra of Some of the Synthesized Compounds

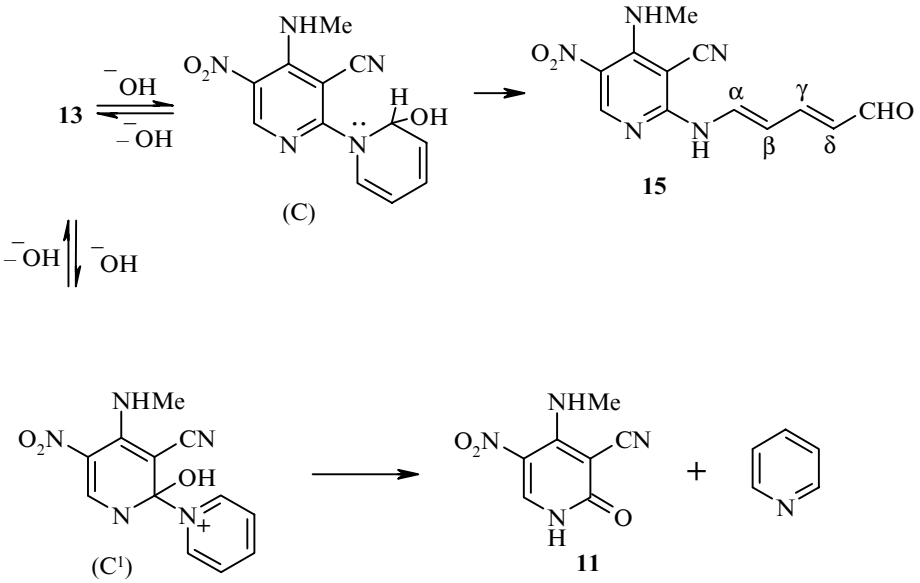
Compound	Chemical shifts, δ, ppm. (*J*, Hz)
6	1.41 (6H, d, *J* = 7.2, CH($\underline{CH_3}$)$_2$); 2.54 (3H, s, 6-CH_3); 4.50 (1H, m, $\underline{CH}(CH_3)_2$); 8.68 (1H, s, 2-H)
8	2.48 (3H, s, 6-CH_3); 3.59 (3H, s, 1-CH_3); 8.42 (1H, s, 2-H)
10	2.83 (3H, s, NH$\underline{CH_3}$); 5.84 (1H, d, *J* = 7.2, 5-H); 7.36 (1H, d, 6-H); 7.24 (1H, br. s, $\underline{NH}CH_3$); 11.02 (1H, br. s, NH)
11	3.30 (3H, d, *J* = 6.4, NH$\underline{CH_3}$); 8.74 (1H, s, 6-H); 8.80 (1H, q, N$\underline{H}CH_3$); 12.5 (1H, br. s, 1-NH)
17	1.19 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$); 3.34 (3H, d, *J* = 6.4, NH$\underline{CH_3}$); 4.12 (2H, q, $\underline{CH_2}CH_3$); 4.14 (2H, s, SCH_2); 8.94 (1H, s, 6-H); 8.96 (1H, q, $NHCH_3$)
18	1.28 (3H, t, *J* = 7.2, $CH_2\underline{CH_3}$); 2.92 (3H, s, NH$\underline{CH_3}$); 4.27 (2H, q, $\underline{CH_2}CH_3$); 6.99 (2H, br. s, NH_2); 8.02 (1H, br. s, NH); 8.83 (1H, s, 6-H)

The main tendencies linked with substitution or opening of the pyridine ring are therefore unchanged in comparison with those observed in [4], in spite of the presence of an additional electron-donating group in position 4.

Summing up the data obtained, it is possible using compound **13** as an example, to refine the probable reasons for the phenomena observed.



The rate of attack of anion at the α-position of the pyridinium ring is greater due to the wholenumbered positive charge and the more stable neutral molecule (A) compared with the zwitter-ion (B). However the stabilization of (A) is hindered (the medium is alkaline and protonation is slowed), while (B) is stabilized irreversibly with the splitting away of a pyridine molecule. A different picture is observed on treating the pyridinium salt with anions containing an atom of hydrogen [$^-$OH or $HC^-(CN)_2$].



In this case intermediate C is characterized by a rapid and irreversible prototropic shift of the OH [or $HC(CN)_2$] group proton to the pyridinium ring nitrogen accompanied by opening of the ring. This type of stabilization proved to be the most effective, but the other, similar to that observed on obtaining compound **17** (C^1 pyridone), does not take place in practice.

In conclusion we note that the presence in position 4 of an additional functional group, a methylamino group, opens new possibilities for various heterocyclizations. One of them was effected in the present work. Heating bicyclic compound **18** with ethyl orthoformate leads to the formation of a pyrimidine ring involving the 3-NH_2 and 4-NHMe groups. The thienopyrimidine derivative **19** was obtained as a result. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 (3H, t) and 4.31 (2H, q) from the COOEt group; 3.39 (3H, s, N-CH_3); 8.07 (1H, s, 4-H); 8.86 (1H, s, 7-H).

The data of elemental analysis and NMR spectra of the substances obtained are given in Tables 1 and 2.

EXPERIMENTAL

The IR spectra for nujol suspensions were recorded on a Perkin–Elmer 457 instrument. The ^{1}H NMR spectra were obtained on a Varian Unity 400 (400 MHz) spectrometer, solvent was DMSO-d_6. The mass spectra were recorded on a MAT 112 instrument with direct insertion of samples into the ion source. The purity of substances and the reaction times were checked by TLC on Silufol UV 254 plates in the system methanol–benzene, 2:8, visualizing in UV light.

α-Cyano-β-isopropylaminocrotonic Acid Amide (4). A mixture of amide **3** (7.7 g, 50 mmol), isopropylamine (13 ml, 150 mmol), and methanol (50 ml) was boiled for 2 h. The reaction mixture was cooled, the solid filtered off, and compound **4** was obtained.

5-Cyano-1-isopropyl-6-methyl-1,4-dihydro-4-pyrimidinone (6). A mixture of compound **4** (3.34 g, 20 mmol) and acetal **5** (10 ml) in DMF (15 ml) was boiled for 8 h. The DMF was evaporated in vacuum, a 5% solution of sodium hydroxide (130 ml) was added to the residue, the mixture boiled for 1 h, cooled, and acidified with hydrochloric acid to pH 6-7. The precipitate of compound **6** was filtered off, washed with water, and dried.

α-Cyano-β-(N-methylamino)crotonic Acid Amide (7). A mixture of compound **3** (7.3 g, 47 mmol) and a 33% solution of methylamine in alcohol (90 ml) was stored for 24 h at 20°C. The precipitate was filtered off, washed with alcohol, dried, and compound **7** was obtained. The same compound was obtained previously in [6].

5-Cyano-1,6-dimethyl-1,4-dihydro-4-pyrimidinone (8). A solution of compound **7** (1.4 g, 10 mmol) and compound **5** (8 ml) in isopropyl alcohol (10 ml) was boiled for 8 h. The mixture was cooled, the solid filtered off, and washed with alcohol.

5-Cyano-6-(N,N-dimethylaminovinyl)-1-methyl-1,4-dihydro-4-pyrimidinone (9). A mixture of compound **8** (2.8 g, 20 mmol) and compound **5** (18.3 ml, 100 mmol) was boiled for 6 h. The mixture was cooled, filtered, and the solid was washed with alcohol.

3-Cyano-4-methylamino-2-pyridone (10). Compound **9** (4.08 g, 20 mmol) was boiled with 5% aqueous sodium hydroxide solution (130 ml) for 1 h. The mixture was cooled, acidified with hydrochloric acid to pH 6-7, the precipitate of pyridone **10** was filtered off, washed with water, and dried.

2-Cyano-4-methylamino-5-nitro-1,2-dihydro-2-pyridone (11). Compound **10** (7.5 g, 50 mmol) was stirred in conc. H_2SO_4 (40 ml) at 20°C, after which the reaction mixture was cooled to 0-2°C and nitric acid (*d* 1.5) (9 ml) was added dropwise at the same temperature. The mixture was stirred for 2 h at 0-2°C then for 1 h at 20°C. The reaction mixture was poured onto ice (250 g), and left for 1 h. The solid was filtered off, washed with ice water, and dried.

2-Chloro-3-cyano-4-methylamino-5-nitropyridine (1). A mixture of compound **11** (2.5 g, 38 mmol), triethylamine hydrochloride (3.9 g, 28 mmol), and phosphorus oxychloride (20 ml) was boiled for 3 h. The excess of phosphorus oxychloride was evaporated in vacuum. The residue was treated with ice (100 g) and made alkaline with sodium hydroxide solution to pH 7. The precipitate of compound **1** was filtered off, washed with water, and dried.

5-Imino-4-methylamino-3-nitrodipyrimido[1,2-*a*:3,2-*c*]pyrimidine (12). 2-Aminopyridine (1.44 g, 16 mmol) was added to a solution of compound **1** (2.34 g, 11 mmol) in acetonitrile (35 ml). The reaction mixture was stirred for 4 h at 20°C, the precipitate of compound **12** was filtered off, and washed with cold acetonitrile.

1-(3-Cyano-4-methylamino-5-nitro-2-pyridyl)pyridinium Chloride (13). A mixture of compound **1** (12 g, 10 mmol) and pyridine (3.8 g, 47 mmol) in acetonitrile (40 ml) was stirred for 3.5 h at 20°C. The precipitate of salt **13** was filtered off, and washed with cold acetonitrile.

3-Cyano-2-ethoxycarbonylmethylthio-4-methylamino-5-nitropyridine (17). Thioglycolic acid ethyl ester (0.9 ml, 7.5 mmol) and sodium acetate (0.6 g, 7.5 mmol) were added to a solution of salt **13** (1.6 g, 5.5 mmol) in methanol (70 ml). The reaction mixture was stirred for 1 h at 20°C, the precipitate of compound **17** was filtered off, washed with cold methanol, and with water, and dried.

3-Amino-2-ethoxycarbonyl-4-methylamino-5-nitrothieno[2,3-*b*]pyridine (18). Sodium ethylate (0.06 g Na in 10 ml absolute alcohol) was added dropwise with stirring to a suspension of compound **17** (0.6 g, 2 mmol) in absolute alcohol (40 ml), and the mixture was heated to form a solution. The mixture was then cooled, the precipitate of **18** was filtered off, and washed with alcohol.

2-Amino-3-cyano-4-methylamino-5-nitropyridine (14). Piperidine (12.7 ml, 126 mmol) was added to a solution of salt **13** (2.5 g, 86 mmol) in water (25 ml). The mixture was boiled for 5 min, cooled, acetone (10 ml) was added, the mixture was filtered, the precipitate of compound **14** was washed with water, and dried.

6-(3-Cyano-4-methylamino-5-nitro-2-pyridyl)amino -1,1-dicyanohexatriene (16). Malonodinitrile (0.2 g, 2.8 mmol) and triethylamine (0.28 g, 2.8 mmol) were added to a solution of salt **13** (0.75 g, 2.6 mmol) in methanol (50 ml). The reaction mixture was stirred for 1 h at 20°C, the precipitate of **16** was filtered off, and washed with cold methanol.

4-(3-Cyano-4-methylamino-5-nitro-2-pyridyl)amino-1-formylbutadiene (15). A solution of salt **13** (1.5 g, 5 mmol) was stirred with sodium hydroxide (0.2 g, 5 mmol) in water (5 ml) for 2 h at 20°C. The precipitated solid was filtered off, washed with water, dried and butadiene **15** was obtained.

2-Ethoxycarbonyl-5-methyl-6-nitro-1,5-dihydro-1-thia-3,5,8-triaza-acenaphthene (19). A mixture of compound **18** (1 g, 3.4 mmol), ethyl orthoformate (1.06 g, 10 mmol), and acetic anhydride (10 ml) was boiled for 3.5 h, then cooled. The precipitate was filtered off, washed with water to pH 6-7, dried, and tricyclic compound **19** was obtained.

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