

# Synthesis of *N*-Methylmorpholinium 1-Amino-2,4-dicyano-4-phenylcarbamoyl(ethoxycarbonyl)-1,3-butadiene-1-thiolates and Their Transformation into Pyridine-2-thiol Derivatives

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**Abstract**—Condensation of ethyl 2-cyano-3-ethoxypropenoate and 2-cyano-3-ethoxy-*N*-phenylpropenamide with cyanothioacetamide and *N*-methylmorpholine gave *N*-methylmorpholinium 1-amino-2,4-dicyano-4-phenylcarbamoyl(ethoxycarbonyl)-1,3-butadiene-1-thiolates which were converted into pyridine-2-thiol derivatives: *N*-methylmorpholinium pyridine-2-thiolate, 2-alkylthiopyridines, and thieno[2,3-*b*]pyridine.

Synthesis of new nicotinic acid derivatives attracts interest primarily from the viewpoint of searching for biologically active compounds. In particular, nicotinic acid amides are effective in the treatment of Alzheimer's disease [1], and some its esters exhibit herbicide properties [2]. While developing new approaches to pyridine derivatives possessing amide and ester functionalities [3], we have studied reactions of 2-cyano-3-ethoxypropenoic acid ester and amide **Ia** and **Ib** with cyanothioacetamide (**II**) and *N*-methylmorpholine. These reactions resulted in formation of *N*-methylmorpholinium 1-amino-2,4-dicyano-4-phenylcarbamoyl(ethoxycarbonyl)-1,3-butadiene-1-thiolates **III** which were converted into pyridine derivatives **V** via alkylation with halogen derivatives (pathway *a* in Scheme 1). This reaction is interesting due to the fact that cyclization of salts **III** yields just 5-phenylcarbamoyl(ethoxycarbonyl)-6-aminopyridines **V** rather than 5-cyano-6-oxopyridines. It is known that ethyl 3-aryl-2-cyanopropenoates react with cyanothioacetamide to give 4-aryl-3,5-dicyano-6-hydroxypyridine-2(1*H*)-thione [4]; ethyl cyano(cyclohexylidene)acetate and cyanothioacetamide give rise to 6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-4-spirocyclohexane-2-thiolate [5]; and condensation of formaldehyde, ethyl cyanoacetate, and cyanothioacetamide leads to formation of 6-oxo-3,5-dicyano-1,4,5,6-tetrahydropyridine-2-thiolate [6]. In these cases the cyano group was not involved in the cyclization to pyridine ring. By contrast, salts **III** undergo cyclization with

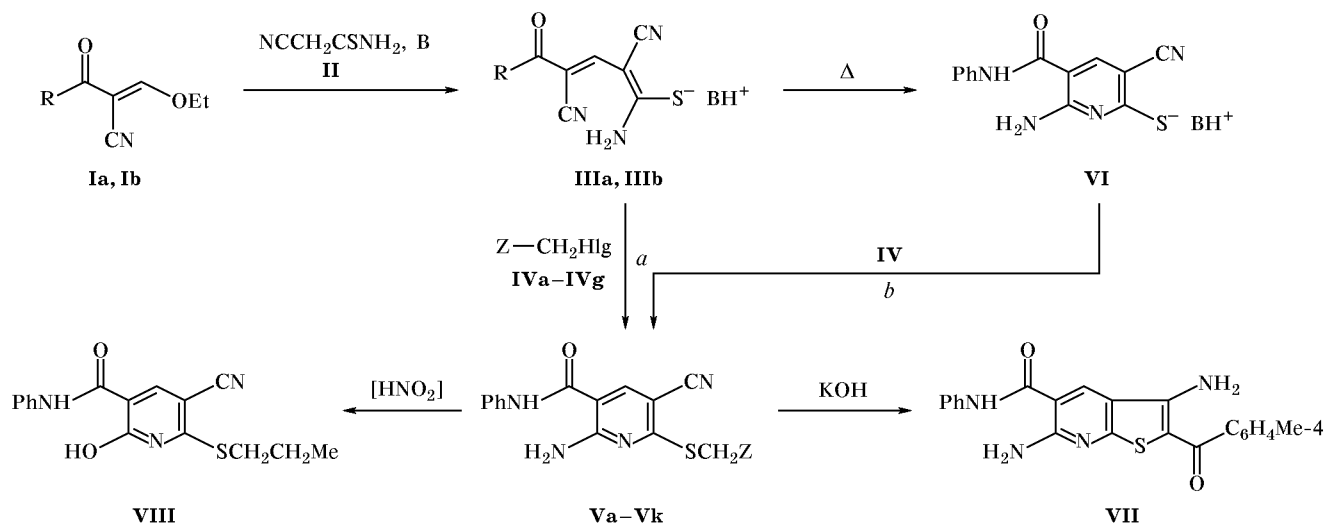
participation of the cyano group. Presumably, compounds **I** and **II** react following the nucleophilic vinyl substitution mechanism ( $S_NVin$ ) [7] according to which the initial configuration is often retained [8]. This means that alkene **I** exists as *E*-isomer which endows salt **III** with a configuration favorable for cyclization to aminopyridines **V**. By heating of salt **IIIa** in ethanol we obtained pyridinethiolate **VI**, and alkylation of the latter with halogen derivatives **IV** gave 2-pyridyl sulfides **V** (pathway *b* in Scheme 1).

The structure of compounds **V** and **VI** was proved by spectral data (Tables 1, 2) and chemical transformations. Treatment of **Va** with alkali gave substituted thienopyridine **VII**, and diazotization of aminopyridine **Vb** afforded the corresponding hydroxy derivative **VIII**.

## EXPERIMENTAL

The IR spectra were recorded on an IKS-29 spectrometer in mineral oil. The  $^1H$  NMR spectra were obtained on Bruker DR-500 (500.13 MHz; compounds **Va**, **Vb**, **Vd**, **Ve**, and **VII**), Gemini-200 (199.975 MHz; compounds **IIIa**, **Vc**, **Vf**, **Vg**, **Vk**, **VI**, and **VIII**), and Bruker WP-100SY spectrometers (100 MHz; compounds **IIIb**, **Vh**, **Vi**, and **Vj**) in DMSO- $d_6$  using TMS as internal reference. The mass spectra (70 eV) were run on a Kratos MS-890 mass spectrometer. The melting points were determined on a Koeffler device. The progress of reactions was

Scheme 1.



B = *N*-methylmorpholine; **I**, **III**, R = PhNH (**a**); EtO (**b**); **IV**, Hlg = Br, Z = CH=CH<sub>2</sub> (**a**), Et (**b**); Hlg = I, Z = H (**c**); Hlg = Cl, Z = CONH<sub>2</sub> (**d**); Hlg = Br, Z = 4-MeC<sub>6</sub>H<sub>4</sub>CO (**e**), 4-BrC<sub>6</sub>H<sub>4</sub>CO (**f**), Pr (**g**); **V**, R = PhNH, Z = 4-MeC<sub>6</sub>H<sub>4</sub>CO (**a**), Et (**b**), CH=CH<sub>2</sub> (**c**), H (**d**), CONH<sub>2</sub> (**e**); R = EtO, Z = 4-BrC<sub>6</sub>H<sub>4</sub>CO (**f**), CH=CH<sub>2</sub> (**g**), Et (**h**), H (**i**), Pr (**j**), 4-MeC<sub>6</sub>H<sub>4</sub>CO (**k**).

monitored, and the purity of products was checked, by TLC on Silufol UV-254 plates using acetone-hexane as eluent; development with iodine vapor.

***N*-Methylmorpholinium 1-amino-2,4-dicyano-4-phenylcarbamoyl-1,3-butadiene-1-thiolate (IIIa).** *N*-Methylmorpholine, 2.2 ml (20 mmol), was added at 20°C to a suspension of 1 g (10 mmol) of cyanothioacetamide (**II**) in 15 ml of ethanol. The mixture was stirred for 5 min, and it became homogeneous. Compound **Ia**, 2.16 g (10 mmol), was added, and the

mixture was stirred for 10 min. It turned dark, and a solid precipitated. The mixture was left to stand for 24 h, and compound **IIIa** was filtered off and washed with ethanol and acetone. Yield 2.6 g (71%), mp 122–124°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3245, 3378, 3494 (NH<sub>2</sub>); 2190, 2205 (C≡N); 1678 (CONH); 1647 (δNH<sub>2</sub>). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 2.77 s (3H, CH<sub>3</sub>), 3.22 m (4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.70 m (4H, CH<sub>2</sub>OCH<sub>2</sub>), 6.99–7.71 m (5H, H<sub>arom</sub>), 9.13 s (1H, CH=), 8.33 br.s and 9.62 br.s (2H, NH<sub>2</sub>), 10.34 s

**Table 1.** Yields, melting points, and elemental analyses of substituted pyridines **Va–Vk**

Comp. no.	Yield, <sup>a</sup> %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
<b>Va</b>	81 (76)	235–237 (EtOH)	65.39	4.42	14.07	C <sub>22</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S	65.65	4.51	13.92
<b>Vb</b>	73 (65)	170–172 (EtOH)	61.63	4.98	18.12	C <sub>16</sub> H <sub>16</sub> N <sub>4</sub> OS	61.52	5.16	17.93
<b>Vc</b>	68 (59)	180–181 (EtOH)	62.15	4.40	17.86	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub> OS	61.92	4.55	18.05
<b>Vd</b>	72 (63)	210–212 (AcOH)	58.88	4.11	19.86	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> OS	59.14	4.25	19.70
<b>Ve</b>	81 (67)	225–227 (EtOH)	54.87	3.79	21.58	C <sub>15</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub> S	55.04	4.00	21.39
<b>Vf</b>	70	224–226 (AcOH)	48.30	3.14	10.15	C <sub>17</sub> H <sub>14</sub> BrN <sub>3</sub> O <sub>3</sub> S	48.58	3.36	9.99
<b>Vg</b>	82	120–123 (AcOH)	54.82	5.09	15.77	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	54.74	4.98	15.96
<b>Vh</b>	76	120–122 (EtOH)	54.29	5.59	16.03	C <sub>12</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	54.32	5.70	15.84
<b>Vi</b>	70	149–151 (AcOH)	50.54	4.39	17.93	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	50.62	4.67	17.71
<b>Vj</b>	65	180–182 (EtOH)	56.11	5.84	14.93	C <sub>13</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	55.89	6.13	15.04
<b>Vk</b>	79	195–196 (AcOH)	60.70	5.01	12.11	C <sub>18</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S	60.83	4.82	11.82

<sup>a</sup> According to method *b*; the yields obtained by method *a* are given in parentheses.

Table 2. IR and  $^1\text{H}$  NMR spectra of compounds Va–Vk

Comp. no.	IR spectrum, $\nu$ , $\text{cm}^{-1}$			$^1\text{H}$ NMR spectrum, $\delta$ , ppm					
	$\text{NH}_2$	$\delta\text{NH}_2$	$\text{C}\equiv\text{N}$ , $\text{C}=\text{O}$	4-H, s	$\text{NH}_2$ , br.s	CONH, s, or $\text{OCH}_2$ , q	Ph or $\text{CH}_3\text{CH}_2$ , t	$\text{SCH}_2$	Z
Va	3300	1645	2200, 1698	8.42	7.89	10.11	7.12 t (1H), 7.35 t (2H), 7.69 d (2H)	4.95 s	2.41 s (3H, $\text{CH}_3$ ), 7.38 d (2H, $\text{H}_{\text{arom}}$ ), 7.99 d (2H, $\text{H}_{\text{arom}}$ )
Vb	2295– 3360	1662	2210, 1683	8.40	8.03	10.09	7.11 t (1H), 7.34 t (2H), 7.69 d (2H)	3.25 t	1.01 t (3H, $\text{CH}_3$ ), 1.70 m (2H, $\text{CH}_2$ )
Vc	3303, 3368, 3484	1655	2204, 1700	8.42	8.00	9.98	7.04 t (1H), 7.28 t (2H), 7.66 d (2H)	3.90 d	5.12 d (1H, $=\text{CH}_2$ , $^3J_{\text{cis}} = 9.5$ Hz), 5.38 d (1H, $=\text{CH}_2$ , $^3J_{\text{trans}} = 17.2$ Hz), 5.96 m (1H, $\text{CH}=\text{}$ )
Vd	3315, 3360, 3472	1650	2203, 1674	8.41	8.08	10.10	7.11 t (1H), 7.32 t (2H), 7.68 d (2H)	2.56 s	–
Ve	3305, 3364, 3500	1650	2210, 1702	8.43	8.02	10.11	7.12 t (1H), 7.35 t (2H), 7.69 d (2H)	3.89 s	7.49 br.s and 7.18 br.s (2H, $\text{NH}_2$ )
Vf	3310, 3444	1620	2207, 1690	8.17	7.95	4.26	1.36	4.84 s	7.67 d (2H, $\text{H}_{\text{arom}}$ ), 8.00 d (2H, $\text{H}_{\text{arom}}$ )
Vg	3300, 3413	1622	2219, 1695	8.15	7.98 br.d	4.28	1.35	3.88 d	5.12 d (1H, $=\text{CH}_2$ , $^3J_{\text{cis}} = 9.9$ Hz), 5.37 d (1H, $=\text{CH}_2$ , $^3J_{\text{trans}} = 16.0$ Hz), 5.90 m (1H, $\text{CH}=\text{}$ )
Vh	3300, 3420, 3540	1608	2215, 1710	8.22	8.02 br.d	4.26	1.30	3.21 t	0.99 t (3H, $\text{CH}_3$ ), 1.68 m (2H, $\text{CH}_2$ )
Vi	3248, 3355, 3450	1650	2200, 1692	8.22	8.10 br.d	4.25	1.31	2.57 s	–
Vj	3342, 3496	1645	2214, 1683	8.23	8.12 br.d	4.26	1.30	3.42 t	0.90 t (3H, $\text{CH}_3$ ), 1.22–1.75 m [4H, ( $\text{CH}_2$ ) <sub>2</sub> ]
Vk	3302, 3426	1618	2209, 1690	8.18	7.95 br.d	4.28	1.35	4.87 s	2.44 s (3H, $\text{CH}_3$ ), 7.35 d and 7.95 d (4H, $\text{H}_{\text{arom}}$ )

(1H, NH). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 270 (13), 210 (36), 176 (100), 149 (48), 132 (35), 101 (30), 93 (35), 43 (58). Found, %: C 58.03; H 5.54; N 18.92.  $\text{C}_{18}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$ . Calculated, %: C 58.20; H 5.70; N 18.85.

**N-Methylmorpholinium 1-amino-2,4-dicyano-4-ethoxycarbonyl-1,3-butadiene-1-thiolate (IIIb)** was synthesized as described above for salt IIIa using

ester **Ib** as initial compound. Yield 2.2 g (68%), mp 113–117°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3212, 3420 ( $\text{NH}_2$ ); 2174, 2191 ( $\text{C}\equiv\text{N}$ ); 1678 ( $\text{C}=\text{O}$ ); 1653 ( $\delta\text{NH}_2$ ).  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 1.19 t (3H,  $\text{CH}_3$ ), 2.81 s (3H,  $\text{NCH}_3$ ), 3.20 m (4H,  $\text{CH}_2\text{NCH}_2$ ), 3.78 m (4H,  $\text{CH}_2\text{OCH}_2$ ), 4.08 q (2H,  $\text{CH}_2$ ), 7.52 br.s and 8.30 br.s (2H,  $\text{NH}_2$ ), 8.66 s (1H,  $\text{CH}=\text{}$ ). Mass spectrum,  $m/z$  ( $I_{\text{rel}}$ , %): 223 (36), 196 (82), 150 (100), 123

(18), 101 (14), 43 (19). Found, %: C 52.02; H 6.13; N 17.18.  $C_{14}H_{20}N_4O_3S$ . Calculated, %: C 51.84; H 6.21; N 17.27.

**2-Amino-5-cyano-6-(Z-methylthio)nicotinic acid anilides and esters Va–Vk.** *a.* Alkyl halide **IV**, 5 mmol, was added to a solution of 5 mmol of salt **IIIa** or **IIIb** in 8 ml of DMF. The mixture spontaneously warmed up to 40–45°C and was stirred for 1 h. The precipitate was filtered off and washed with ethanol and hexane. The yields, melting points, and spectral parameters of products **Va–Vk** are given in Tables 1 and 2.

*b.* Alkyl halide **IV**, 10 mmol, was added to a solution of 3.71 g (10 mmol) of salt **VI** in 12 ml of DMF, and the mixture was stirred for 1 h. The precipitate was filtered off and washed with ethanol and hexane. Products **Va–Ve** thus obtained were identical (in melting points and TLC data) to those prepared as described in *a.*

**6-Allylthio-2-amino-5-cyano-N-phenylnicotinamide (Vc).** Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 310 [ $M$ ]<sup>+</sup> (81), 295 (27), 218 (96), 177 (22), 93 (60), 65 (24), 41 (100).

**Ethyl 2-amino-5-cyano-6-(4-methylbenzoyl-methylthio)nicotinate (Vk).** Mass spectrum,  $m/z$  ( $I_{rel}$ , %): 355 [ $M$ ]<sup>+</sup> (23), 119 (100), 91 (28), 65 (9).

**N-Methylmorpholinium 6-amino-3-cyano-5-phenylcarbamoylpyridine-2-thiolate (VI).** A solution of 3.71 g (10 mmol) of salt **IIIa** in 20 ml of ethanol was heated to the boiling point and was left to stand for 24 h at room temperature. The precipitate of salt **VI** was filtered off and washed with acetone. Yield 2.5 g (67%), mp 130–132°C. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3180, 3303, 3397 (NH<sub>2</sub>); 2190 (C≡N); 1681 (CONH); 1647 ( $\delta$ NH<sub>2</sub>). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 2.82 s (3H, CH<sub>3</sub>), 3.21 m (4H, CH<sub>2</sub>NCH<sub>2</sub>), 3.74 m (4H, CH<sub>2</sub>OCH<sub>2</sub>), 7.02–7.55 m (5H, H<sub>arom</sub>), 8.17 br.s (2H, NH<sub>2</sub>), 9.02 s (1H, CH), 10.18 br.s (1H, CONH). Found, %: C 57.98; H 5.63; N 19.04.  $C_{18}H_{21}N_5O_2S$ . Calculated, %: C 58.20; H 5.70; N 18.85.

**3,6-Diamino-2-(4-methylbenzoyl)thieno[2,3-*b*]pyridine-5-carboxanilide (VII).** To a solution of 2 g (5 mmol) of compound **Va** in 8 ml of DMF we added 2.8 ml (5 mmol) of 10% aqueous KOH, and the mixture was stirred for 1 h. It was then diluted with 10 ml of water, and the precipitate was filtered off and washed with water, ethanol, and hexane. Yield 1.75 g (87%), mp 260–262°C (from AcOH). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3295, 3414 (NH<sub>2</sub>); 1720 (C=O); 1700 (CONH); 1633 ( $\delta$ NH<sub>2</sub>). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 2.89 s (3H, CH<sub>3</sub>), 7.11–7.42 m (7H, H<sub>arom</sub>, 3-NH<sub>2</sub>), 7.65 d and 7.73 d (4H, H<sub>arom</sub>), 8.28 br.s (2H, 6-NH<sub>2</sub>), 8.79 s (1H,

CH), 10.33 br.s (1H, CONH). Found, %: C 65.42; H 4.33; N 14.13.  $C_{22}H_{18}N_4O_2S$ . Calculated, %: C 65.65; H 4.51; N 13.92.

**5-Cyano-6-hydroxy-N-phenyl-6-propylthionotinamide (VIII).** A solution of 0.07 g (0.96 mmol) of NaNO<sub>2</sub> in 1 ml of concentrated sulfuric acid was added dropwise with stirring to a suspension of 0.2 g (0.64 mmol) of compound **Vb** in 5 ml of glacial acetic acid. The mixture was adjusted to pH 7 by adding a saturated aqueous solution of sodium acetate, and the precipitate was filtered off and washed with water, ethanol, and hexane. Yield 0.15 g (75%), mp 218–220°C (from AcOH). IR spectrum,  $\nu$ ,  $cm^{-1}$ : 3395 (OH), 2228 (C≡N), 1684 (CONH). <sup>1</sup>H NMR spectrum,  $\delta$ , ppm: 1.02 t (3H, CH<sub>3</sub>), 1.70 m (2H, CH<sub>2</sub>), 3.29 t (2H, SCH<sub>2</sub>), 7.06–7.63 m (5H, H<sub>arom</sub>), 8.46 s (1H, CH), 11.03 br.s (1H, NHCO); no OH signal was observed, presumably due to fast exchange with water present in the solvent. Found, %: C 61.45; H 5.03; N 14.12.  $C_{16}H_{15}N_3O_2S$ . Calculated, %: C 61.32; H 4.82; N 13.41.

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