ONE-STEP SYNTHESIS OF 2-AMINO-3-FURANCARBOXYLIC ACID DERIVATIVES FROM 2-FURANCARBALDEHYDE

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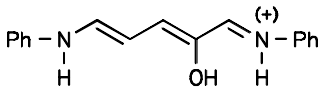
Reaction of derivatives of 2-furancarbaldehyde or 2-acetylfuran with malononitrile, methyl cyanoacetate or cyanoacetamide in the presence of secondary amines afforded derivatives of 2-amino-3-furancarboxylic acid in 45 – 88% yields.

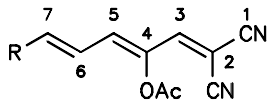
Iminium salts of 1,5-diarylamino-2-hydroxy-2,4-pentadienal[1] (*I*) are important intermediates in the synthesis of *N*-arylpyrrol-2-carbaldehydes[2,3], *N*-aryl-3-hydroxypyridinium salts[4,5] or 2,4-diarylamino-2-cyclopentenones[6–8] . The present study concerns the synthetic utilization of reactive intermediates arising in the base-induced opening of 2-substituted furan derivatives for the preparation of polysubstituted aminofuran compounds.

Reaction of iminium salt of 1,5-dianilino-2-hydroxy-2,4-pentadienal (*I*) with malononitrile in pyridine afforded 2-amino-5-(*E*)-(4,4-dicyano-1,3-butadienyl)-3-furancarbonitrile (*VIIa*) in 62% yield. In an attempt to increase the yield of compound *VIIa*, we performed the reaction of compound *I* with malononitrile in a mixture of pyridine and acetic anhydride (1 : 6). However, subsequent reaction of the obtained 5-(*N*-phenylacetamido)-2-acetoxy-2,4-pentadienylidenemalononitrile (*IIa*) with malononitrile and morpholine did not give the compound *VIIa* but, instead, a nucleophilic substitution product, 5-morpholin-1-yl-2-acetoxy-2,4-pentadienylidenemalononitrile (*IIb*). Similarly unsuccessful were also the reactions of compound *I* with methyl cyanoacetate or cyanoacetamide: instead of the expected aminofuran derivatives *VIIb* and *VIIc* we obtained only cyclopentenones *IIIa* and *IIIb*.

The aminofuran derivative *VIIa* was obtained by reaction of 2-furancarbaldehyde (*IVa*) with malononitrile in the presence of amine in molar ratio 1 : 2 : 1 (with aniline the yield was 11%, with morpholine 88%).

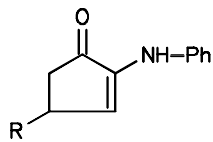


I



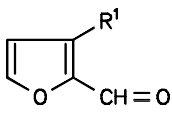
IIa, R = Ph–N(Ac)

IIb, R = 



IIIa, R = NHPh

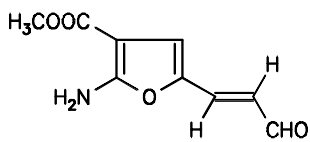
IIIb, R = 



IVa, R^1 = H

IVb, R^1 = Br

IVc, R^1 = CH_3

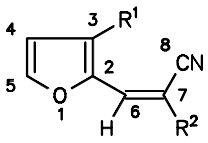


VI

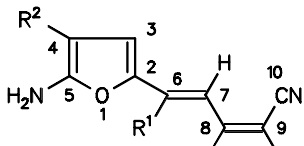
Under the same conditions, aldehyde *IVa* reacted with methyl cyanoacetate or cyanoacetamide to give methyl 2-amino-5-[(1*E*,3*E*)-4-cyano-4-methoxycarbonyl-1,3-butadienyl]-3-furancarboxylate (*VIIb*) or 2-amino-5-[(1*E*,3*E*)-4-aminocarbonyl-4-cyano-1,3-butadienyl]-3-furancarboxamide (*VIIc*). The aminofurans *VIIa* – *VIIc* were prepared also from the condensation products *Va* – *Vc*.

Similarly reacted the 3-bromo- and 3-methyl-substituted 2-furancarbaldehydes *IVb* and *IVc* or their condensation products *Vd* – *Vi* with malonic acid derivatives under formation of aminofurans *VIId* – *VIIi*. Reaction of compound *Vd* with malononitrile

gave compound *VIId* and 2-imino-5-(1-bromo-3-morpholin-1-yl-2-propenylidene)-2,5-dihydrofuran-3-carbonitrile (*VIII*) which is probably an intermediate in the conversion of compound *Vd* into compound *VIId*. On reaction with malononitrile in methanol the compound *VIII* was converted almost quantitatively into compound *VIId* (as evidenced by ^{1}H NMR spectrum and TLC).



V

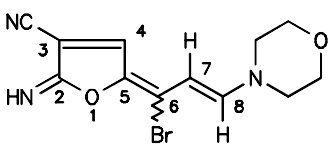


VII

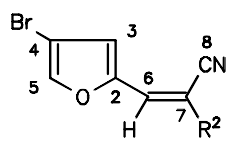
In formulae *V* and *VII* :

	R^1	R^2
a	H	CN
b	H	$COOCH_3$
c	H	$CONH_2$
d	Br	CN
e	Br	$COOCH_3$
f	Br	$CONH_2$
g	CH_3	CN
h	CH_3	$COOCH_3$
i	CH_3	$CONH_2$

Under the described reaction conditions, 4-bromo-2-furancarbaldehyde gave only condensation products *IXa – IXc* and 5-bromo-2-furancarbaldehyde was converted into a secondary amine by nucleophilic substitution of the bromine atom[9].

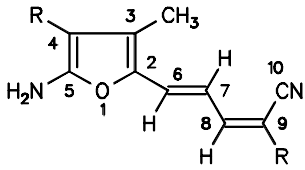


VIII



IXa, R^2 = CN
IXb, R^2 = $COOCH_3$
IXc, R^2 = $CONH_2$

Using the method of opening and recyclization of the furan ring, we prepared polysubstituted 2-aminofuran derivatives *XIa* and *XIb* by reaction of 2-acetylfuran (*X*) with malononitrile or cyanoacetamide in the presence of pyrrolidine.



XIa, R = CN

XIb, R = $CONH_2$

The structure of the synthesized compounds was determined on the basis of ^1H and ^{13}C NMR spectra, IR spectra and elemental analysis; compound *VIIa* was also prepared by an independent synthesis[16]. Vicinal coupling constants in the spectrum of compound *VIIa* (^3J(C-3,H-6) = 0 Hz; ^3J(C-10,H-8) = 12.4 Hz; ^3J(R^2,H-8) = 7.0 Hz and ^3J(C-6,H-8) = 4.4 Hz) and compound *IIb* (^3J(C-3,H-6) = 0 Hz, ^3J(C-10,H-8) = 12.4 Hz; ^3J(R^2,H-8) = 7.6 Hz and ^3J(C-6, H-8) = 4.4 Hz) have shown that the configuration of the multiple bonds is 1*E*,3*E* (refs[10,11]).

The described synthetic method makes possible the synthesis of derivatives of 2-amino-3-furancarboxylic acid from 2-furancarbaldehyde or 2-acetylfuran by opening and recyclization of the furan ring.

EXPERIMENTAL

The melting points were determined on a Kofler block Boetius and are uncorrected. UV spectra were measured in methanol on an M-40 (Zeiss, Jena) spectrophotometer; concentration 1 . 10^{-4} mol dm^3, ε values are given in m^2 mol^{-1}. IR spectra were recorded on a PU 9800 FTIR Philips analytical spectrometer in KBr pellets (wavenumbers in cm^{-1}). Proton (300 MHz) and ^{13}C NMR (75.05 MHz) spectra were obtained with a Varian VXR-300 instrument at 25 °C in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. 3-Bromofuran was prepared according to ref.[12], 3-methyl-2-furancarbaldehyde (*IVc*) according to ref.[13], 2-cyano-3-(2-furyl)propenenitrile (*Va*), methyl (*E*)-2-cyano-3-(2-furyl)propenoate (*Vb*) and (*E*)-2-cyano-3-(2-furyl)propenamide (*Vc*) according to ref.[10].

2-Amino-5-[(*E*)-4,4-dicyano-1,3-butadienyl]-3-furancarbonitrile (*VIIa*)

1,5-Bis(phenylamino)-2-hydroxypentamethinium chloride (*I*; 3 g, 0.01 mol) was added in one portion to a solution of malononitrile (2.0 g, 0.03 mol) in pyridine (10 ml). After stirring and heating at 70 – 80 °C for 10 min, the mixture was allowed to cool slowly to ambient temperature. The deposited precipitate was filtered, washed with ice-cold methanol and crystallized from methanol; yield 1.3 g (62%) of compound *VIIa*. For the physicochemical characteristics see Tables I, II and V.

2,4-Bis(phenylamino)-2-cyclopentenone (*IIIa*)

A. Salt *I* (3.0 g, 0.01 mol) was added in one portion to a solution of methyl cyanoacetate (3.0 g, 0.03 mol) in pyridine (10 ml). After stirring and heating at 70 °C for 30 min, the mixture was cooled to room temperature and poured into water (200 ml). The solid was collected on filter and purified

TABLE I
Yields, melting points and elemental analyses of compounds *Vd – Vi*, *VIIa – VIIi* and *IXa – IXc*

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found				IR spectrum, cm^{-1}	
			% C	% H	% Br	% N	ν(C≡N)	ν(C=O)
Vd	167 – 168 89	$C_8H_3BrN_2O$ (223.0)	43.08 42.92	1.36 1.21	35.83 35.78	12.56 12.42	2 222	–
Ve	132 – 134 81	$C_9H_6BrNO_3$ (256.1)	42.22 42.09	2.36 2.21	31.21 31.16	5.47 5.35	2 228	1 657
Vf	189 –192 86	$C_8H_5BrN_2O_2$ (241.0)	39.86 39.74	2.09 1.93	33.15 33.08	11.62 11.52	2 226	1 660
Vg	123 – 124 91	$C_9H_6N_2O$ (158.2)	68.35 68.21	3.82 3.74	–	17.71 17.66	2 230	–
Vh	90 – 93 79	$C_{10}H_9NO_3$ (191.2)	62.82 62.75	4.74 4.64	–	7.33 7.24	2 236	1 652
Vi	160 – 161 83	$C_9H_8N_2O_2$ (176.2)	61.36 61.29	4.58 4.50	–	15.90 15.84	2 233	1 649
VIIa	222 – 224 88	$C_{11}H_6N_4O$ (210.2)	62.86 62.79	2.88 2.69	–	26.65 26.58	2 220	1 606
VIIb	228 – 228 65	$C_{13}H_{12}N_2O_5$ (276.3)	56.52 56.46	4.38 4.28	–	10.14 10.04	2 203	1 686
VIIc	240 – 244 47	$C_{11}H_{10}N_4O_3$ (246.2)	53.66 53.57	4.09 4.01	–	22.75 22.69	2 205	1 655
VIId	217 – 219 79	$C_{11}H_5BrN_4O$ (289.1)	45.70 45.61	1.74 1.66	27.64 27.58	19.38 19.25	2 200	1 600
VIIe	179 – 181 62	$C_{13}H_{11}BrN_2O_5$ (355.2)	43.97 43.88	3.12 3.06	22.50 22.44	7.89 7.82	2 230	1 663
VIIf	243 – 246 45	$C_{11}H_9BrN_4O$ (293.1)	45.07 44.97	3.09 2.98	27.26 27.20	19.11 19.07	2 210	1 649
VIIg	199 – 201 76	$C_{12}H_8N_4O$ (224.2)	64.28 64.21	3.60 3.53	–	24.99 24.90	2 220	–
VIIh	177 – 179 55	$C_{11}H_{14}N_2O_5$ (290.3)	57.93 57.88	4.86 4.79	–	9.65 9.58	2 221	1 651
VIIi	244 – 246 45	$C_{12}H_{12}N_4O_3$ (260.3)	55.38 55.31	4.65 4.59	–	21.53 21.48	2 219	1 653

TABLE I
(*Continued*)

Compound	M.p., °C Yield, %	Formula (M.w.)	Calculated/Found				IR spectrum, cm^{-1}	
			% C	% H	% Br	% N	ν(C≡N)	ν(C=O)
IXa	142 – 144 89	$C_8H_3BrN_2O$ (223.0)	43.08 43.02	1.36 1.28	35.83 35.77	12.56 12.51	2 221	–
IXb	139 – 140.5 82	$C_9H_6BrNO_3$ (256.1)	42.22 42.17	2.36 2.31	31.21 31.16	5.47 5.43	2 226	1 653
IXc	186 – 187.5 78	$C_8H_5BrN_2O_2$ (241.0)	39.86 39.81	2.09 2.04	33.15 33.08	11.62 11.57	2 225	1 662

TABLE II
^{1}H NMR spectral parameters for compounds *Vd – Vi* and *IXa – IXc*. Chemical shifts in ppm (δ-scale), coupling constants (*J*) in Hz

Compound	H-3, s	H-4, d *J*(4,5)	H-5, d *J*(5,4)	H-6, s	Other signal
Vd	–	7.19 2.1	8.35 2.1	8.09	
Ve	–	7.16 1.8	8.32 1.8	7.80	3.82 s, 3 H (OCH_3)
Vf	–	7.07 1.7	8.21 1.7	7.77	7.92 bs, 2 H (NH_2)
Vg	–	6.76 1.5	8.16 1.5	8.27	
Vh	–	6.75 1.8	8.12 1.8	7.93	2.26 s, 3 H (CH_3) 3.82 s, 3 H (OCH_3)
Vi	–	6.69 1.5	8.03 1.5	7.85	2.23 s, 3 H (CH_3)
IXa	7.57	–	8.28[a]	8.08	
IXb	7.58	–	8.20[a]	8.07	3.91 s, 3 H (OCH_3)
IXc	7.46	–	8.12[a]	7.99	7.08 bs, 2 H (NH_2)

[a] Singlets.

by crystallization from benzene; yield 0.85 g (33%) of *IIIa*, m.p. 141 – 142 °C (decomp.); reported[7] m.p. 140 – 143 °C and m.p. 144 °C (ref.[6]).

B. Cyanoacetamide (2.5 g, 0.03 mol) reacted with the salt *I* (3.0 g, 0.01 mol) as described in procedure *A*; yield of compound *IIIa* was 1.0 g (39%), m.p. 141 – 142 °C.

2-Phenylamino-4-(piperidin-1-yl)-2-cyclopentenone (*IIIb*)

A. Salt *I* (3.0 g, 0.01 mol) was added in one portion to a solution of methyl cyanoacetate (3.0 g, 0.03 mol) and piperidine (2.6 g, 0.03 mol) in pyridine (10 ml) and the reaction mixture was treated as described for the preparation of compound *IIIa*. Yield 1.8 g (68%) of *IIIb*, m.p. 121 – 123 °C (reported[14] m.p. 123 – 124 °C).

B. Reaction of cyanoacetamide (2.5 g, 0.03 mol) with the salt *I* (3.0 g, 0.01 mol) according to procedure *A* afforded 1.5 g (57%) of the product, m.p. 121 – 123 °C.

2-Acetoxy-5-(*N*-phenylacetamido)-2,4-pentadienylidenemalononitrile (*IIa*)

A. Malononitrile (0.8 g, 0.012 mol) was dissolved in a mixture of acetic acid (20 ml), pyridine (1.5 ml) and acetic anhydride (10 ml). The salt *I* (3.0 g, 0.01 mol) was rapidly added portionwise to the vigorously stirred mixture. After stirring at room temperature for 24 h, the mixture was poured into ice-cold water (100 ml), the solid material was filtered, washed with water, dilute methanol and crystallized from methanol. Yield 2.88 g (90%) of compound *IIa*, m.p. 188 – 190 °C. For $C_{18}H_{15}N_3O_3$ (321.3) calculated: 67.28% C, 4.71% H, 13.08% N; found: 67.06% C, 4.65% H, 13.19% N. ^{1}H NMR spectrum: 1.85 s, 3 H ($NCOCH_3$); 1.94 s, 3 H ($OCOCH_3$); 4.78 dd, 1 H (H-6, *J*(5,6) = 12.0, *J*(6,7) = 14.0); 7.23 d, 1 H (H-5, *J*(5,6) = 12); 7.86 s, 1 H (H-3); 7.31 – 7.62 m, 5 H (arom. H); 8.23 d, 1 H (H-7, *J*(7,6) = 14.0). ^{13}C NMR spectrum: 19.4 q (CH_3); 23.1 q (CH_3); 72.9 s (C-2); 114.8 s (2 × CN); 104.7 d (C-6); 128 d (C-2′ and C-6′); 129.4 d (C-4′); 130.2 d (C-3′ and C-5′); 139.5 s (C-1′); 137.8 s (C-4); 140.5 d (C-5); 143.7 d (C-3); 153.3 d (C-7); 167.5 s (N–C=O); 169.0 s (O–C=O).

B. Malononitrile (0.8 g, 0.012 mol) was dissolved in a suspension of sodium acetate (1.7 g, 0.02 mol) and acetic anhydride (30 ml). Salt *I* (3.0 g, 0.01 mol) was added in portions to the vigorously stirred mixture. After 24 h, the mixture was processed as described in the procedure *A*. Yield 1.93 g (60%) of *IIa*.

2-Acetoxy-5-(morpholin-1-yl)-2,4-pentadienylidenemalononitrile (*IIb*)

A solution of morpholine (0.87 g, 0.01 mol) in methanol (5 ml) was added to a vigorously stirred suspension of compound *IIa* (3.21 g, 0.01 mol) in dry methanol (100 ml). After several minutes the mixture became homogeneous and a solid deposited. After stirring for 2 h the solid was collected, washed with ice-cold methanol and purified by crystallization from methanol. Yield 2.1 g (77%) of compound *IIb*, m.p. 165 – 167 °C. For $C_{14}H_{15}N_3O_3$ (273.3) calculated: 61.53% C, 5.53% H, 15.38% N; found: 61.49% C, 5.48% H, 15.35% N. ^{1}H NMR spectrum: 2.1 s, 3 H ($OCOCH_3$); 3.38 – 3.75 m, 8 H (4 × CH_2 of morpholine); 5.44 m, 1 H (H-6); 6.98 d, 1 H (H-5, *J*(5,6) = 12.0); 7.26 s, 1 H (H-3); 7.52 d, 1 H (H-7, *J*(7,6) = 12.0). ^{13}C NMR spectrum: 20.2 q (CH_3); 46.0 t (2 × NCH_2); 53.5 t (2 × OCH_2); 55.3 s (C-2); 116.9 s (CN); 118.5 s (C-1); 96.0 d (C-6); 133.2 s (C-4); 147.5 d (C-5); 147.7 d (C-3); 158.2 d (C-7); 168.4 s (C=O).

General Procedure for Preparation of Nitriles *VIIa*, *VIId*, *VIIg*, Methyl Esters *VIIb*, *VIIe*, *VIIh*, and Amides *VIIc*, *VIIf* and *VIIi*

A. The corresponding aldehyde (0.01 mol), and the methylene component (0.02 mol) were dissolved in methanol (15 ml) and a solution of the secondary amine (0.01 mol, morpholine, piperidine or pyrrolidine) in methanol (3 ml) was added under vigorous stirring. After a short exothermic reaction, the solution was stirred at room temperature for 3 h and then allowed to stand at 0 °C for 12 h. After acidification with dilute acetic acid, the deposited solid was collected and purified by crystallization from methanol.

B. The corresponding compound *Va – Vi* (0.01 mol) was dissolved in methanol (10 ml) and the methylene component (0.01 mol) was added. The mixture was vigorously stirred and a solution of the secondary amine (0.01 mol; morpholine, piperidine or pyrrolidine) in methanol (3 ml) was added. The reaction mixture was worked up as described for procedure *A*. For physicochemical and spectral characteristics of compounds *VIIa – VIIi* see Tables I, III and V.

5-[(2*E*)-1-Bromo-(3-morpholin-1-yl)-2-propenylidene]-2-imino-2,5-dihydrofuran-3-carbonitrile (*VIII*)

The title compound was obtained by reaction of compound *IVb* (1.75 g, 0.01 mol) with malononitrile (1.32 g, 0.02 mol) and morpholine (0.87 g, 0.01 mol) as described in procedure *A* of the preceding experiment. The reaction mixture was subjected to chromatography on silica gel L100/250 in benzene–ethyl acetate (5 : 1) and then in ethyl acetate; yield 0.38 g (12.3%) of compound *VIII*, m.p. 167 – 169 °C. For $C_{12}H_{12}BrN_3O_2$ (310.2) calculated: 46.47% C, 3.90% H, 25.76% Br, 13.55% N; found: 46.21% C, 3.79% H, 25.58% Br, 13.50% N. ^{1}H NMR spectrum: 3.35 m, 4 H (NCH_2); 3.69 m, 4 H (OCH_2); 5.65 d, 1 H (H-7, *J*(7,8) = 12.6); 7.26 s, 1 H (H-4); 7.57 d, 1 H (H-8, *J*(8,7) = 12.6); 8.20 s, 1 H (NH). ^{13}C NMR spectrum: 49.77 t (NCH_2); 65.57 t (OCH_2); 69.22 s (C-3); 99.48 d (C-7); 114.93 s (CN); 117.96 s (C-6); 124.19 d (C-4); 132.15 s (C-5); 157.71 d (C-8); 165.73 s (C-2).

Reaction of Compound *VIII* with Malononitrile

A solution of compound *VIII* (320 mg, 1 mmol) in methanol (5 ml) was warmed to 45 °C. Malononitrile (100 mg, 1.5 mmol) in methanol (2 ml) was added in one portion and the mixture was refluxed for 30 min. After cooling and standing at 0 °C for 12 h, the solid was filtered, washed with a small amount of methanol and purified by crystallization from methanol to give 185 mg (65%) of compound *VIId*.

2-Amino-4-methyl-[(*E*)-4,4-dicyano-1,3-butadienyl]-3-furancarbonitrile (*XIa*)

A. A solution of pyrrolidine (0.71 g, 0.01 mol) in methanol (3 ml) was added at once to a vigorously stirred solution of (*Z*)-2-cyano-3-methyl-3-(2-furyl)propenenitrile[10] (1.5 g, 0.01 mol) in methanol (10 ml). After stirring for 2 min, a solution of malononitrile (0.7 g, 0.01 mol) in methanol (5 ml) was added and stirring was continued for 10 min. The mixture was acidified with dilute acetic acid, the precipitate was collected and crystallized from methanol. Yield 1.45 g (65%) of compound *XIa*. For physicochemical characteristics and NMR spectra see Tables I, II and IV.

B. 2-Acetylfuran (1.1 g, 0.01 mol), malononitrile (1.33 g, 0.02 mol) and pyrrolidine (0.7 g, 0.01 mol) in methanol (10 ml) reacted as described under *A*; yield 1.05 g (47%) of compound *XIa*.

C. The same procedure as described under *A*, applied to 2-acetylfuran (1.1 g, 0.01 mol), malononitrile (1.33 g, 0.02 mol) and sodium ethoxide (0.68 g, 0.01 mol) in ethanol (10 ml), afforded 0.92 g (41%) of compound *XIa*, m.p. 266 – 270 °C (decomp.). For $C_{12}H_8N_4O$ (224.2) calculated: 64.28% C, 3.60% H, 24.99% N; found: 64.15% C, 3.51% H, 25.10% N. ^{1}H NMR spectrum: 6.38 dd, 1 H (H-7, *J*(8,7) = 12.0, *J*(7,6) = 14.0); 7.33 d, 1 H (H-6, *J*(7,6) = 14.0); 7.89 d, 1 H (H-8, *J*(8,7) = 12.0); 8.91 m,

2 H (NH_2); 2.14 s, 3 H (CH_3). ^{13}C NMR spectrum: 9.8 q (CH_3); 70.8 s (C-9); 75.4 s (C-4); 112.8 d (C-7); 114.1 s (CN); 115.8 s (C-10); 132.2 d (C-6); 137.9 s (C-2); 139.3 s (C-3); 160.1 d (C-8); 165.8 s (C-5).

2-Amino-4-methyl-5-[(1*E*,3*E*)-4-cyano-4-aminocarbonyl-1,3-butadienyl]-3-furancarboxamide (*XIb*)

A solution of 2-acetylfuran (1.1 g, 0.01 mol), cyanoacetamide (1.9 g, 0.02 mol) and pyrrolidine (0.71 g, 0.01 mol) in ethanol (10 ml) was refluxed for 3 h. After standing at room temperature for 12 h and at 0 °C for 5 h, the deposited precipitate was collected, washed with anhydrous methanol and dried; yield 0.47 g (18%) of compound *XIb*, m.p. 278 – 280 °C (decomp.). For $C_{12}H_{12}N_4O_3$ (260.3) calculated: 55.38% C, 4.65% H, 21.53% N; found: 55.16% C, 4.70% H, 21.62% N. ^1H NMR spectrum: 2.20 s, 3 H (CH_3); 6.41 dd, 1 H (H-7, J(8,7) = 12.0, J(7,6) = 14.0); 6.69 bs, 2 H ($CONH_2$); 7.21 d, 1 H (H-6, J(6,7) = 14.0); 7.25 bs, 2 H ($CONH_2$); 7.80 d, 1 H (H-8, J(8,7) = 12.0). ^{13}C NMR spectrum: 9.8 q, (CH_3); 95.2 s (C-9); 100.9 s (C-4); 114.4 d (C-7); 115.4 s (C-10); 116.8 s ($CONH_2$); 129.1 s (C-3); 132.2 d (C-6); 139.6 s (C-2); 151.8 d (C-8); 165.3 s (C-5).

TABLE III
^1H NMR spectral parameters for compounds *VIIa* – *VIIi*. Chemical shifts in ppm (δ-scale), coupling constants (J) in Hz

Compound	H-3, s	H-6, d J(6,7)	H-7, dd J(7,6), J(7,8)	H-8, d J(8,7)	Other signals
VIIa	7.47	7.14 14.1	6.50 12.3; 14.1	8.06 12.3	8.84 bs, 2 H (NH_2)
VIIb	7.18	7.27 14.1	6.54 12.1; 14.1	8.03 12.1	3.71 s, 3 H (OCH_3) 3.75 s, 3 H (OCH_3) 8.22 bs, 2 H (NH_2)
VIIc	7.27	7.07 14.7	6.50 12.3; 14.7	7.88 12.6	7.81 bs, 2 H (NH_2) 7.42 m, 4 H (2 × NH_2)
VIId	7.89	–	7.39 12.0	8.52 12.0	9.56 s, 2 H (NH_2)
VIIe	7.31	–	6.90 12.0	8.03 12.0	3.72 s, 3 H (OCH_3) 3.79 s, 3 H (OCH_3) 8.42 bs, 2 H (NH_2)
VIIf	7.66	–	6.87 11.7	7.98 11.7	7.99 bs, 2 H (NH_2) 7.99 bs, 2 H (NH_2)
VIIg	7.61	–	6.59 12.6	8.24 12.6	2.20 s, 3 H (CH_3) 8.70 bs, 2 H (NH_2)
VIIh	7.42	–	6.65 12.9	8.12 12.9	2.21 s, 3 H (CH_3) 3.72 and 3.77 s, 2 × 3 H (2 × OCH_3) 8.12 s, 2 H (NH_2)
VIIi	7.45	–	6.62 12.3	8.03 12.3	2.16 s, 3 H (CH_3) 6.92 bs, 2 H (NH_2) 7.35 – 7.72 b, 4 H (2 × NH_2)

3-Bromo-2-furancarbaldehyde (*IVb*)

Phosphorus oxychloride (16.1 g, 0.105 mol) was added dropwise at 0 °C to a stirred solution of 3-bromofuran (14.7 g, 0.1 mol) and *N*,*N*-dimethylformamide (8.0 g, 0.11 mol). The mixture was allowed to stand at room temperature for 1 h, heated at 80 °C for 2 h, cooled, poured on ice (1 kg) and neutralized with solid potassium carbonate. After standing for 2 h, the deposited oil was separated, the aqueous layer extracted with ether (2 × 100 ml), and the combined organic layers were dried. The solvent was evaporated and the product was distilled in vacuo. Fraction b.p. 89 – 90 °C/1.6 kPa was collected, yield 15.1 g (86%) of compound *IVb* (reported[15] b.p. 97 – 98 °C/1.8 kPa.

General Procedure for Preparation of 2-Cyano-(3-bromo-2-furyl)propenenitrile (*Vd*), Methyl (*E*)-2-Cyano-(3-bromo-2-furyl)propenoate (*Ve*) and (*E*)-2-Cyano-(3-bromo-2-furyl)propenamide (*Vf*)

Malononitrile, methyl cyanoacetate or cyanoacetamide (25 mmol) was dissolved in methanol (5 ml) and sodium methoxide (27 mg, 0.5 mmol) was added. 3-Bromo-2-furancarbaldehyde (4.4 g, 25 mmol) in methanol (3 ml) was added in one portion to the vigorously stirred mixture. After stirring at room temperature for 2 h, the mixture was decomposed with water (0.2 ml) and allowed to stand at 0 °C for 12 h. The solid was collected, washed with water and purified by crystallization from aqueous ethanol. For physicochemical and spectral characteristics of the obtained compounds *Vd* – *Vf* see Tables I, II and IV.

General Procedure for Preparation of 2-Cyano-(3-methyl-2-furyl)propenenitrile (*Vg*), Methyl (*E*)-2-Cyano-(3-methyl-2-furyl)propenoate (*Vg*) and (*E*)-2-Cyano-(3-methyl-2-furyl)propenamide (*Vi*)

Malononitrile, methyl cyanoacetate or cyanoacetamide (25 mmol) was dissolved in methanol (10 ml) and triethylamine (several drops) was added. The mixture was heated at 50 °C and 3-methyl-2-furancarbaldehyde (2.75 g, 25 mmol) in methanol (3 ml) was added. After heating at reflux for 15 min,

TABLE IV
^{13}C NMR chemical shifts (ppm, δ-scale) of compounds *Vd* – *Vi* and *IXa* – *IXc*

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	R^2
Vd	145.6	116.6	118.1	151.6	140.4	76.8	114.4	113.5 (CN)
Ve[a]	145.2	115.4	117.4	150.8	131.2	98.4	114.8	162.8 (COO)
Vf	145.4	115.8	116.9	149.3	131.4	102.8	112.5	162.2 (CON)
Vg[b]	145.2	138.8	116.7	150.8	141.6	72.4	115.1	113.8 (CN)
Vh[c]	144.7	137.1	116.5	149.7	135.9	94.6	115.6	163.2 (COO)
Vi[d]	144.6	133.9	115.9	148.1	132.5	99.4	116.6	163.2 (CON)
IXa	149.9	126.0	104.1	148.9	143.9	79.6	113.3	114.5 (CN)
IXb[e]	150.3	124.4	101.0	147.8	139.0	103.7	115.3	163.1 (COO)
IXc	150.7	122.6	104.0	146.7	136.5	103.3	116.5	162.1 (CON)

[a] Other signal: 53.1 (OCH_3). [b] Other signal: 10.4 (CH_3). [c] Other signals: 53.0 (OCH_3); 10.4 (CH_3). [d] Other signal: 10.3 (CH_3). [e] Other signal: 53.6 (OCH_3).

water (0.5 ml) was added and the mixture was set aside at 0 °C for 12 h. The solid was collected and crystallized from aqueous ethanol. For physicochemical and spectral characteristics of the products *Vg – Vi* see Tables I, II and IV.

General Procedure for Preparation of 2-Cyano-(4-bromo-2-furyl)propenenitrile (*IXa*), Methyl (*E*)-2-Cyano-(4-bromo-2-furyl)propenoate (*IXb*) and (*E*)-2-Cyano-(4-bromo-2-furyl)propenamide (*IX*c)

The title compounds were prepared from 4-bromo-2-furancarbaldehyde[17] in the same manner as described for the preparation of compounds *Vg – Vi* in the preceding experiment. For physicochemical and spectral characteristics of the products *IXa – IXc* see Tables I, II and IV.

Methyl (*E*)-2-Amino-5-(3-oxopropenyl)furan-3-carboxylate[16] (*VI*)

Methyl 2-cyano-3-(2-furyl)propenoate (5.3 g, 0.02 mol) was added in one portion under stirring into piperidine (20 ml). After the exothermic reaction had subsided, the deep-red mixture was stirred at room temperature for 30 min. After standing for 12 h, the viscous solution was poured under vigorous stirring into water (500 ml). The separated solid was collected, washed with dilute methanol and crystallized from methanol. Yield 2.4 g (41%) of compound *VI*; m.p. 173 – 174 °C. For $C_9H_9NO_4$ (195.2) calculated: 55.39% C, 4.65% H, 7.18% N; found: 55.11% C, 4.47% H, 7.82% N. ^{1}H NMR spectrum: 9.48 d, 1 H (CH=O, J = 8.0); 7.91 bs, 1 H (NH_2); 7.31 d, 1 H (H-6, J(6,7) = 15.1); 7.19 s, 1 H (H of furan); 6.10 dd, 1 H (H-7, J(7,8) = 8.0, J(6,7) = 15.1; 3.75 s, 3 H (OCH_3).

Independent Synthesis of Compound *VIIb* from *VI*

Compound *VI* (1.95 g, 0.01 mol) and methyl cyanoacetate (1.1 g, 0.011 mol) were dissolved in *N*,*N*-dimethylformamide (20 ml) at 35 °C and piperidine (3 drops) was added with stirring. The mixture was stirred for 5 h, poured into water (100 ml), the solid was collected, washed with dilute methanol and crystallized from methanol. Yield 2.15 g (78%) of compound *VIIb*.

TABLE V
^{13}C NMR chemical shifts (ppm, δ-scale) of compounds *VIIa – VIIi*

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	R^2
VIIa	140.4	126.6	73.5	166.5	134.1	114.8	160.4	72.3	113.6	114.2; 115.3 (2 × CN)
VIIb[a]	140.6	122.9	96.3	164.7	134.5	114.6	155.5	93.0	115.8	162.9; 163.2 (2 × COO)
VIIc	139.6	120.0	100.9	165.3	132.3	114.4	151.7	95.2	116.8	163.3; 164.0 (2 × CON)
VIId	138.8	127.2	76.3	166.2	126.3	113.4	156.0	73.3	113.2	113.5; 114.6 (2 × CN)
VIIe[b]	139.0	123.8	99.6	165.0	126.7	113.2	150.9	93.9	115.6	162.6; 162.7 (2 × COO)
VIIf	138.2	121.8	104.1	162.1	124.2	112.8	147.7	96.0	116.6	164.6; 165.0 (2 × CON)
VIIg[c]	142.2	123.4	73.7	166.1	142.7	113.3	156.1	71.6	115.8	113.6; 114.2 (2 × CN)
VIIh[d]	142.3	120.5	96.0	164.5	142.4	112.6	150.5	92.7	116.1	163.1; 164.5 (2 × COO)
VIIi[e]	141.5	117.2	101.5	165.4	139.2	112.5	146.4	94.7	117.0	163.7; 163.8 (2 × CON)

[a] Other signals: 50.9; 52.5 (2 × OCH_3). [b] Other signals: 51.0; 52.9 (2 × OCH_3). [c] Other signal: 13.5 (CH_3). [d] Other signals: 13.5 (CH_3); 50.8; 52.5 (2 × OCH_3). [e] Other signal: 13.5 (CH_3).

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