Substitution of Halogens on Furan by Hydrazines
Stable Derivatives of 5-Hydrazinofuran

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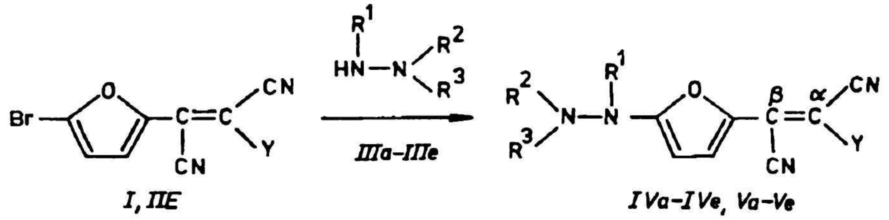
Selected alkyl- and arylhydrazines displace bromine at furan in (5-bromo-2-furyl)ethylenetricarbonitrile and in the novel methyl (*E*)-3-(5-bromo-2-furyl)-2,3-dicyanopropenoate to give the corresponding 5-hydrazino-substituted nitriles and propenoates. Some spectral properties of the prepared compounds are discussed.

Methods of preparation of hydrazones of the furan series, compounds known to possess antifungal and antimicrobial [1—3] as well as tuberculostatic properties [4], have been thoroughly investigated. In contrast, derivatives possessing a hydrazino group directly attached to the furan ring have, due to their instability leading to ring-opening and eventual formation of derivatives of pyridazine [5—7] or pyrazole [8], so far not been prepared. Only some derivatives of (2-furylalkyl)-hydrazine have been known [9, 10].



I, IVa–IVe: Y = CN

IIE, Va–Ve: Y = $COOCH_3$

III–V	R^1	R^2	R^3
a	H	H	C_6H_5
b	H	H	*p*-CH_3–C_6H_4
c	H	H	*p*-CH_3O–C_6H_4
d	H	CH_3	CH_3
e	CH_3	H	H

Scheme 1

In our earlier papers we presented (5-bromo-2-furyl)ethylenetricarbonitrile *I* [11] as a reactive furan derivative and used it to prepare stable (alkylamino)furan derivatives [12]. The reason for the stability of the latter compounds lies in the presence of one of the strongest electron-accepting groups ($\sigma_p(\mathrm{C(CN)}{=}\mathrm{C(CN)_2}) = 1.70$ [13]) in their molecules. In addition, the amino group in the target (alkylamino)furans contributes, together with the cyano group in the ethylene side chain, to the stability of such "push-pull" systems [12].

We investigated reactivity of the tricarbonitrile *I* and that of the analogous methyl (*E*)-3-(5-bromo-2-furyl)-2,3-dicyanopropenoate *IIE* in the reactions with substituted alkyl- and arylhydrazines, respectively. A nucleophilic displacement of bromine atom in position 5 of the furan ring led to the formation of stable hydrazinofurans (Scheme 1).

Methyl 3-(5-bromo-2-furyl)-2-cyanopropenoate, when first treated with NaCN and then oxidized with lead tetraacetate under conditions similar to those used in the preparation of *I* [11], furnished methyl 3-(5-bromo-2-furyl)-2,3-dicyanopropenoate *II* as a mixture of *E* and *Z* isomers. The ratio *E/Z* in which isomers were formed de-

Table 1. Dependence of the Position of λ_{max}/nm of Derivatives *IVa*, *Va* on the Relative Permittivity of the Solvent

Parameter		Solvent					
		Heptane	CCl_4	$CHCl_3$	Acetone	CH_3OH	DMSO
ε_r [14]		1.88	2.24	4.81	20.70	32.70	46.68
λ_{max}	*IVa*	515.5	523.0	531.9	535.0	534.2	548.2
	Va	514.4	518.7	530.8	534.2	531.9	545.8

pended on reaction conditions (temperature, reaction time) and varied from 3 : 1 to 2 : 1 (inferred from ^1H NMR measurements). In order to obtain pure (major) *E* isomer, the reaction mixture was treated with $AlCl_3$ and the complex was decomposed by water, a procedure during which the less stable *Z* isomer decomposed and pure *IIE* could be isolated. The structure assignment of *IIE* was based on elemental analysis, IR, UV, and ^1H and ^{13}C NMR spectral data. The assignment of ^{13}C NMR signals of the cyano groups was facilitated by model *IIE*, containing a ^{13}C-enriched β-CN group. The bathochromic shifts of λ_{max} in UV spectra of compound *IIE* in comparison with those of *I* and chemical shifts of C-5 in ^{13}C NMR spectra indicate lower reactivity of halogen atom of the compound *IIE* in nucleophilic reactions.

A reaction of bromofurylethylenes *I* or *II* with a mole excess of substituted hydrazines gives rise to stable substituted (5-hydrazino-2-furyl)ethylenetricarbonitriles *IVa*—*IVe* and methyl (*E*)-3-(5-hydrazino-2-furyl)-2,3-dicyanopropenoates *Va*—*Ve*, respectively. The reaction is facile with either alkylhydrazines, or with arylhydrazines substituted by donor substituents at the aryl ring. The above-mentioned lower reactivity of halogen in *IIE* was also reflected in the fact that the yields of derivatives *Va*—*Ve* were lower than those of derivatives *IVa*—*IVe*. Hydrazobenzene did not react under the reaction conditions; at elevated temperatures trinitrile *I* reacted with hydrazobenzene to give products of disproportionation of hydrazobenzene, (5-anilino-2-furyl)ethylenetricarbonitrile (*VI*) and azobenzene.

The structures of the prepared compounds were inferred from the spectral data (IR, UV, ^1H and ^{13}C NMR). The prepared hydrazinofurans *IVa*—*IVe* and *Va*—*Ve* are deeply coloured crystalline compounds with strong bands at λ = 520—540 nm in UV spectra. These maxima are only to a small extent influenced by the substituent carried by the hydrazino group. Compounds *IV* and *V* also show a significant positive solvatochromism (Table 1) and, similarly as (5-amino-2-furyl)ethylenetricarbonitriles, increased values of the coupling constants in ^1H NMR spectra [12]. These facts testify to the presence of a marked stabilization by the push-pull mechanism. The electron-acceptor effect of the cyanopropenoate group —C(CN)=C(CN)$COOCH_3$ being lower than that of the tricyanoethylene moiety —C(CN)=$C(CN)_2$ accounts for the red-shifted UV maxima of *IIE* *vs.* *I* and of those of *V* *vs.* *IV*. The presence of the β-cyano group in both types of the furylethylene system invokes a sufficient stabilization by the push-pull effect.

Table 2. Physicochemical Characteristics of the Derivatives *IVa*—*IVe*, *Va*—*Ve*

Compound Y	Formula^a M_r	M.p./°C Yield/%	λ_{max}/nm log {ε}	$\tilde{\nu}(\nu(N—H))$ cm^{-1}	$\tilde{\nu}(\nu(C\equiv N))$ cm^{-1}
IVa	$C_{15}H_9N_5O$	190—193	535	3340	2210
CN	275.3	75	3.56		
IVb	$C_{16}H_{11}N_5O$	189—190	538	3350	2200
CN	289.3	70	3.59		
IVc	$C_{16}H_{11}N_5O_2$	183—186	535	3350	2200
CN	305.3	67	3.55		
IVd	$C_{11}H_9N_5O$	238—240	522	3320	2210
CN	227.2	56	3.87		
IVe	$C_{10}H_7N_5O$	155—157	520	3340	2200
CN	213.2	71	3.74		
Va	$C_{16}H_{12}N_4O_3$	187—190	534.2	3340	2200
$COOCH_3$	308.3	46	3.52		
Vb	$C_{17}H_{14}N_4O_3$	179—181	539.0	3350	2200
$COOCH_3$	322.3	61	3.54		
Vc	$C_{17}H_{14}N_4O_4$	185—188	538.0	3350	2200
$COOCH_3$	338.3	42	3.50		
Vd	$C_{12}H_{12}N_4O_3$	233—236	526.0	–	2200
$COOCH_3$	260.3	46	3.80		
Ve	$C_{11}H_{10}N_4O_3$	225—227	524.1	3320	2200
$COOCH_3$	246.2	46	3.78		

a) All compounds gave satisfactory microanalyses for C, H, and N (within ± 0.3 %).

Nucleophilic substitution of β-cyanofurylethylenes by hydrazines thus constitutes a novel approach to the as yet inaccessible hydrazinofurans.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage. UV spectra of 10^{-3}—10^{-4} mol dm^{-3} solutions of the compounds in acetone were recorded on a Specord M-40 spectrophotometer (Zeiss, Jena), ε values are given in m^2 mol^{-1}. Infrared spectra of KBr discs (0.5 mg of sample and 300 mg of KBr) were measured on a Specord IR 75 or M-40 apparatuses (Zeiss, Jena). ^{1}H NMR spectra were obtained on a Jeol FX 100 (100 MHz) and Varian model VXR 300 (300 MHz) spectrometers, respectively. ^{13}C NMR spectra were taken on a Varian VXR 300 (75.12 MHz) spectrometer. In NMR experiments hexadeuteroacetone solutions with tetramethylsilane as internal standard were measured.

Methyl 3-(5-Bromo-2-furyl)-2,3-dicyanopropenoate (*II*)

To a vigorously stirred solution of methyl 3-(5-bromo-2-furyl)-2-cyanopropenoate (5.1 g; 0.02 mol) in dimethylformamide (25 cm^3), kept at – 10—0 °C, the aqueous solution of NaCN (1.0 g; 0.0204 mol) (2 cm^3) was added. Then acetic acid was added (50 cm^3), followed by lead tetraacetate (9 g; 0.0203 mol), added in small portions within 5 min. The reaction mixture was then stirred for another hour and poured to 400 cm^3 of ice water. The precipitated product was removed by filtration and dried to yield 4.4 g (78 %) of *II* as a mixture of *E* and *Z* isomers in an *n*(*E*) : *n*(*Z*) ratio 3 : 1 to 2 : 1. The crude product, dissolved in dichloro-

Table 3. ^{1}H NMR Spectral Data of Substituted (5-Hydrazino-2-furyl)cyanoethylenes

Compound	δ			
	H-3 (d)	H-4 (d)	$J_{3,4}$/Hz	Others
IVa	7.75	6.25	4.5	7.42—7.65 (m, 5H, phenyl), 2.29 (s, 2H, 2 x NH)
IVb	7.75	6.59	4.5	7.64 (d, 2H, H-2′, H-6′, *J* = 8.4 Hz), 7.31 (d, 2H, H-3′, H-5′, *J* = 8.4 Hz), 2.82 (s, 2H, 2 x NH), 2.37 (s, 3H, CH_3)
IVc	7.73	6.54	4.5	7.67 (d, 2H, H-2′, H-6′, *J* = 9.0 Hz), 7.04 (d, 2H, H-3′, H-5′, J = 9.0 Hz), 3.85 (s, 3H, CH_3), 2.80 (s, 2H, NH)
IVd	7.71	6.42	4.8	3.43 (s, 6H, 2 x CH_3), 2.80 (s, 1H, NH)
IVe	7.66	6.44	4.8	3.63 (s, 3H, CH_3), 2.84 (s, 2H, NH_2)
Va	7.81	6.47	4.5	7.28—7.78 (m, 5H, phenyl), 3.83 (s, 3H, CH_3), 2.91 (s, 2H, NH)
Vb	7.80	6.42	4.5	7.63 (d, 2H, H-2′, H-4′, *J* = 8.4 Hz), 7.29 (d, 2H, H-3′, H-5′, *J* = 8.4 Hz), 3.81 (s, 3H, CH_3—O), 2.81 (s, 2H. NH), 2.37 (s, 3H, CH_3)
Vc	7.77	6.36	4.5	7.65 (d, 2H, H-2′, H-6′, *J* = 9 Hz), 7.03 (d, 2H, H-3′, H-5′, *J* = 9 Hz), 3.85 (s, 3H, CH_3—O), 2.87 (s, 5H, 2 x NH, CH_3)
Vd	7.66	6.21	4.8	3.79 (s, 3H, CH_3—O), 2.77 (s, 2H, NH), 3.37 (s, 6H, 2 x CH_3)
Ve	7.64	6.28	4.5	3.79 (s, 3H, CH_3—O), 2.89 (s, 2H, NH), 3.49 (s, 3H, CH_3)

Table 4. ^{13}C NMR Spectral Data of Selected (5-Hydrazino-2-furyl)cyanoethylenes

Compound	δ							
	C-α	C-β	C-2	C-3	C-4	C-5	CN	Others
IVa	62.3	113.0	140.5	135.0	100.6	161.6	114.1 115.3 115.9	142.8 (C-1′) 124.2 (C-2′, C-6′) 130.5 (C-3′, C-5′) 128.6 (C-4′)
IVb	60.6	114.1	143.1	135.3	102.5	166.9	115.6 116.0 116.6	139.8 (C-1′) 123.5 (C-2′, C-6′) 130.7 (C-3′, C-5′) 138.0 (C-4′) 21.0 (CH_3)
IVd	52.0	114.0	142.8	136.5	100.7	167.9	114.9 116.7 117.0	39.1 (CH_3) 39.14 (CH_3)
IVe	56.5	114.0	143.1	136.2	102.0	169.5	114.2 116.8 117.0	42.0 (CH_3)

ethane (100 cm^3) was then treated with a twofold mass excess of $AlCl_3$, the reaction mixture was stirred for another hour and then poured to 100 cm^3 of ice water. The organic layer was separated, dried with $CaCl_2$ and filtered through a short SiO_2 column in a sintered funnel. After evaporation of solvent 2.5—2.7 g (44—48 %) of *IIE* was obtained, m.p. = 157—159 °C (toluene—heptane, $\varphi_r = 1 \quad 1$).

For $C_{10}H_5BrN_2O_3$ ($M_r = 281.1$) w_i(calc.): 42.7 % C, 1.79 % H, 9.96 % N, 28.4 % Br; w_i(found): 42.8 % C, 1.81 % H, 9.90 % N, 27.9 % Br. UV spectrum, λ_{max}/nm (log {ε}): 388 (3.32). IR spectrum, $\tilde{\nu}/cm^{-1}$: 2955, 2220, 1727, 1530, 1015. ^1H NMR spectrum, δ: 7.83 (d, 1H, H-3), $J = 4.0$ Hz, 6.99 (d, 1H, H-4), $J = 4.0$ Hz, 3.97 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 54.3 (CH_3), 107.1 (C-2), 112.5 (3-CN), 114.6 (2-CN), 118.1 (C-4′), 121.2 (C-3), 126.0 (C-3′), 132.6 (C-5′), 149.5 (C-2′), 161.0 (C-1).

Isomer *IIZ*: ^1H NMR spectrum, δ: 7.55 (d, 1H, H-3), $J = 4.0$ Hz, 6.82 (d, 1H, H-4), $J = 4.0$ Hz, 3.85 (s, 3H, CH_3). ^{13}C NMR spectrum, δ: 54.5 (CH_3), 107.1 (C-2), 113.8 (3-CN), 115.3 (2-CN), 118.0 (C-4′), 121.7 (C-3), 127.3 (C-3′), 132.5 (C-5′), 148.2 (C-2′), 160.9 (C-1).

N-Substituted (5-Hydrazino-2-furyl)cyanoethylenes *IVa*—*IVe*, *Va*—*Ve*

Compound *I* or *IIE* (2 mmol) was dissolved in 30 cm^3 of acetonitrile. The mixture was stirred and within 10 min the hydrazine derivative (4 mmol), dissolved in acetonitrile (30 cm^3) was added at room temperature. The mixture was stirred until a TLC control indicated the consumption of the halo derivative. The precipitated hydrazinium bromide was then removed by filtration and the filtrate subjected to a chromatography on a SiO_2 column, eluted by a toluene—ethyl acetate ($\varphi_r = 3 : 2$) mixture. The isolated products were crystallized from a toluene—heptane mixture. Physicochemical and spectral characteristics of derivatives *IVa*—*IVe* and *Va*—*Ve* are given in Tables 2—4.

Reaction of (5-Bromo-2-furyl)ethylenetricarbonitrile with Hydrazobenzene

(5-Bromo-2-furyl)ethylenetricarbonitrile (0.5 g; 2 mmol) was dissolved in 30 cm^3 of acetonitrile. The solution was stirred, and a solution of hydrazobenzene (0.37 g; 2 mmol) in acetonitrile (30 cm^3) was dropwise added within 10 min. The reaction mixture was stirred under reflux for another hour, whereupon the formed ammonium salt was filtered off and the filtrate separated on a SiO_2 column, eluted by a mixture of toluene and ethyl acetate ($\varphi_r = 3 : 2$). The obtained products were identified as azobenzene (yield 50—60 mg), m.p. = 66—68 °C (ethanol) and (5-anilino-2-furyl)ethylenetricarbonitrile (*VI*) [12]. The yield of *VI* was 0.22 g (43 %), m.p. = 230—235 °C (decomp.). Ref. [12] gives m.p. = 240 °C (decomp.).

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