REACTION OF 2-CYANO-3-(4,5-DIBROMO-2-FURYL)-2-PROPENENITRILE AND METHYL 2-CYANO-3-(4,5-DIBROMO-2-FURYL)-2-PROPENOATE WITH NUCLEOPHILES

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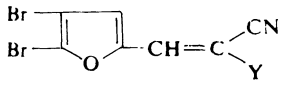
Methyl 2-cyano-3-(4-bromo-5-R-X-2-furyl)-2-propenenitriles and -2-propenoates were prepared from 2-cyano-3-(4,5-dibromo-2-furyl)-2-propenenitrile and methyl 2-cyano-3-(4,5-dibromo-2--furyl)-2-propenoate and the respective nucleophiles R—XNa (X = S, R = C_6H_5, 2-benzimidazolyl, 2-benzothiazolyl, 2-pyrimidinyl, and X = SO_2, R = C_6H_5). The same products also originate by condensation of 4-bromo-5-R-X-2-furaldehydes with malononitrile or methyl cyano acetate under catalysis of alcoholates. Bis(3-bromo-5-formyl-2,2′-furyl) sulfide and bis(5-formyl--2,2′-furyl) sulfide were prepared from 4-X-5-bromo-2-furaldehydes (X = H, Br) with sodium sulfide. 4-Bromo-5-X-2-furaldehydes (X = H, Br) react with sodium hydrogen selenide to give bis-(3-bromo-5-formyl-2,2′-furyl)- or bis(5-formyl-2,2′-furyl) selenides. 2-Cyano-3-(4-bromo-5--amino-2-furyl)-2-propenenitrile and methyl 2-cyano-3-(4-bromo-5-amino-2-furyl)-2-propenoate were synthesized from the corresponding 4,5-dibromo derivatives, sodium azide and malononitrile. All compounds are characterized by UV spectral data; kinetics of nucleophilic substitution reactions with piperidine is presented, as well.

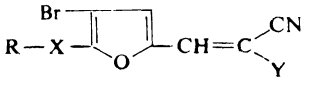
Our preceding papers, concerned reactions of furan derivatives with nucleophilic reagents as arylthio, heteroarylthio, arylsulfonyl, and aryloxy groups, the furan com pounds being 2-cyano-3-(5-arylthio-2-furyl), 2-cyano-3-(5-heteroarylthio-2-furyl), 2-cyano-3-(5-arylsulfonyl-2-furyl), and 2-cyano-3-(5-arylphenoxy-2-furyl)-2-propene-nitriles or -2-propenoates[1-5].

This paper presents the synthesis of 4,5-dibromo-2-furfurylidenemalononitrile (*Ia*) and methyl 4,5-dibromo-2-furfurylidenecyanoacetate (*Ib*) and their reactions with nucleophiles. The former were prepared from 4,5-dibromo-2-furaldehydes and malononitrile or methyl cyanoacetate under the Knoevenagel condensation conditions. A nucleophilic replacement of bromine in *Ia* and *Ib* for sulfur-containing nucleophiles R—XNa (X = S, R = C_6H_5, 2-benzimidazolyl, 2-benzothiazolyl, 2-pyrimidinyl, and X = SO_2, R = C_6H_5) afforded the corresponding 2-cyano-3-(4-bromo-5--R-X-2-furyl)-2-propenenitrile *IIf*—*IIj*, and *IIa*—*IIe*, respectively. To prove the structures, compounds *IIa*—*IIj* were alternatively prepared by Knoevenagel condensation of 4-bromo-5-R-X-2-furaldehydes with malonitrile or methyl cyanoacetate. Both methods afforded compounds *IIa*—*IIj* in high yields. Bis(3-bromo-5-formyl-

-2,2'-furyl) sulfide (*IIIb*) and bis(5-formyl-2,2'-furyl) sulfide (*IIIa*) were prepared from 4,5-dibromo- or 5-bromo-2-furaldehydes and sodium sulfide in water. The same aldehydes gave with sodium hydrogen selenide bis(3-bromo-5-formyl-2,2'-furyl) selenide (*IVb*) and bis(5-formyl-2,2'-furyl) selenide (*IVa*). The aqueous solutions of sodium 5-mercapto- or 5-selenolo-2-furaldehydes, primarily originating, are strongly nucleophilic and react immediately with 5-bromo- or 4,5-dibromofuraldehydes to furnish sulfides *IIIa* and *IIIb* or selenides *IVa* and *IVb*. 4,5-Dibromo-2-furaldehyde and sodium azide in dimethyl sulfoxide gave the corresponding 5-azido derivative, which afforded with malononitrile 2-cyano-3-(4-bromo-5-amino-2-furyl)-2-propenenitrile (*V*). Similarly, methyl 2-cyano-3-(4-bromo-5-amino-2-furyl)-2-propenoate (*VI*) was obtained from *Ib*, sodium azide and malononitrile.



I



II

Ia, Y = CN
Ib, Y = $COOCH_3$

IIa, X = S; R = C_6H_5; Y = $COOCH_3$
IIb, X = S; R = 2-benzimidazolyl-; Y = $COOCH_3$
IIc, X = S; R = 2-benztiazolyl-; Y = $COOCH_3$
IId, X = S; R = 2-pyrimidinyl-; Y = $COOCH_3$
IIe, X = SO_2; R = C_6H_5; Y = $COOCH_3$
IIf, X = S; R = C_6H_5; Y = CN
IIg, X = S; R = 2-benzimidazolyl-; Y = CN
IIh, X = S; R = 2-benztiazolyl-; Y = CN
IIi, X = S; R = 2-pyrimidinyl-; Y = CN
IIj, X = SO_2; R = C_6H_5; Y = CN

Due to entering the lone electron pair of the amino group nitrogen into conjugation with the remaining part of the molecule, and consequently its lower nucleophility, the amino group in derivatives *V* and *VI* does not undergo condensation reactions with carbonyl-containing compounds under usual conditions Physical constants and elemental analysis data of these compounds are listed in Table I.

The electron absorption spectra of compounds *Ia*, *Ib* and *IIa*–*IIj* showed in the UV region three maxima at 205–235 nm, 247–282 nm and 340–376 nm. The first two bands corresponded to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transitions localized in the benzene and furan ring, respectively; the third band was associated with the oscillation of π-electrons along the whole molecule (K-band). The K-band of compounds *IIa*–*IIj* was hypsochromically shifted, when compared with that of the starting substances *Ia* and *Ib*. The last band of amino derivatives *V* and *VI* was shifted into a visible region (458 and 462 nm, respectively).

TABLE I

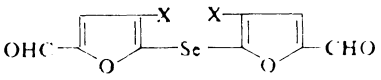
Characteristic data of compounds prepared

Compound	Formula (M_r)	M.p., °C[a] yield, %	Calculated/Found % C	% H	% N	% S	% Br	λ_{max}, nm (log ε)				νC≡N cm^{-1}	νC=O cm^{-1}
Ia	$C_8H_2Br_2N_2O$ (301·9)	138—140 93·6	31·82 31·78	—	9·26 9·25	—	52·93 52·89	212 (3·03)	267 (2·72)	365 (3·44)		2 235	—
Ib	$C_9H_5Br_2NO_3$ (334·9)	168—170 92·3	24·39 24·31	1·49 1·42	3·16 3·14	—	36·04 36·01	207 (3·01)	248 (2·58)	357 (3·44)		2 225	1 728
IIa	$C_{15}H_{10}BrNO_3S$ (364·2)	150—152 89·7	49·46 49·41	2·76 2·68	3·84 3·88	8·80 8·74	21·93 21·89	205 (3·14)	247 (3·17)	340 (3·31)		2 230	1 714
IIb	$C_{16}H_{10}BrN_3O_3S$ (404·2)	208—211 88·7	47·54 47·49	2·49 2·40	10·39 10·35	7·93 7·91	19·76 19·71	205 (3·53)	249 (3·10)	282 (3·17)	361 (3·23)	2 230	1 725
IIc	$C_{16}H_9BrN_2O_3S_2$ (421·2)	141—143 87·5	45·61 45·58	2·15 2·07	6·64 6·67	15·22 15·20	18·96 18·93	224 (3·46)	273 (3·18)	350 (3·31)		2 230	1 725
IId	$C_{13}H_8BrN_3O_3S$ (366·1)	149—151 89·6	42·64 42·61	2·20 2·24	11·47 11·43	8·75 8·70	21·82 21·78	235 (3·25)	277 (2·90)	357 (3·39)		2 237	1 710
IIe	$C_{15}H_{10}BrNO_5S$ (396·2)	181—182 91·5	45·47 45·41	2·54 2·47	3·53 3·59	8·09 8·06	20·16 20·11	208 (3·21)	247 (3·26)	342 (3·41)		2 232	1 723
IIf	$C_{14}H_7BrN_2OS$ (331·1)	125—127 90·1	50·77 50·65	2·13 2·06	8·45 8·41	9·68 9·63	24·12 24·03	210 (3·03)	248 (2·86)	356 (3·44)		2 240	—
IIg	$C_{15}H_7BrN_4OS$ (371·2)	238—240 88·9	48·53 48·49	1·90 1·95	15·09 15·01	8·63 8·60	21·52 21·47	205 (3·52)	251 (3·16)	376 (3·22)		2 235	
IIh	$C_{15}H_6BrN_3OS$ (388·2)	181—183 88·6	46·40 46·35	1·55 1·47	10·82 10·80	16·51 16·48	20·58 20·54	225 (3·49)	275 (3·22)	359 (3·22)		2 232	—

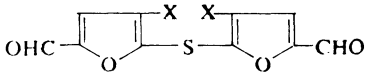
TABLE I
(*Continued*)

Compound	Formula (M_r)	M.p., °C[a] yield, %	Calculated/Found					λ_{max}, nm (log ε)				$\nu C{\equiv}N$ cm^{-1}	$\nu C{=}O$ cm^{-1}
			% C	% H	% N	% S	% Br						
IIi	$C_{12}H_5BrN_4OS$ (333·2)	141—143 86·7	43·26 43·19	1·51 1·54	16·81 16·78	9·62 9·58	23·98 23·94	234 (3·25)	278 (2·90)	363 (3·37)		2 230	—
IIj	$C_{14}H_7BrN_2O_3S$ (363·1)	138—139 91·8	46·29 46·19	1·94 1·90	7·71 7·69	8·82 8·79	22·00 21·93	205 (3·22)	247 (3·29)	347 (3·43)		2 235	—
IIIa	$C_{10}H_6O_4S$ (222·2)	126—128 48·1	54·05 53·91	2·72 2·70	—	14·42 14·39	—	205 (3·05)	225 (2·98)	274 (3·06)	304 (3·24)	—	1 675
IIIb	$C_{10}H_4Br_2O_4S$ (380·0)	111—113 41·3	31·60 31·51	1·06 1·05	—	8·43 8·39	42·05 41·98	226 (3·48)	248 (3·52)	312 (2·42)		—	1 685
IVa	$C_{10}H_6O_4Se$ (269·1)	124—126[b] 50·2	44·63 44·57	2·24 2·19	—	—	—	204 (3·10)	231 (3·01)	271 (3·14)	308 (3·23)	—	1 675
IVb	$C_{10}H_4Br_2O_4Se$ (426·9)	120—122[b] 53·7	28·13 27·86	0i94 0·91	—	—	37·43 37·39	215 (3·11)	234 (3·14)	318 (2·42)		—	1 690
V	$C_8H_4BrN_3O$ (238·0)	231—233 70·8	40·36 40·27	1·69 1·63	17·65 17·59	—	33·56 33·48	225 (3·12)	275 (2·42)	462 (3·45)		2 220	—
VI	$C_9H_7BrN_2R_3$ (271·0)	156—158 67·6	39·87 39·84	2·60 2·54	10·33 10·29	—	29·47 29·41	215 (3·03)	343 (2·59)	458 (3·56)		2 212	1 710

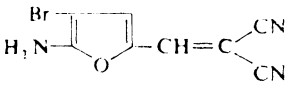
[a] Crystallized from ethanol, [b] crystallized from n-heptane.



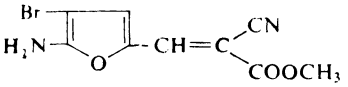
IVa, X = H
IVb, X = Br



IIIa, X = H
IIIb, X = Br



V



VI

This nucleophilic replacement with piperidine was kinetically investigated under conditions of pseudomonomolecular reaction in the excess of the nucleophilic reagent[4,5]. The rate constants k_2 for group replacements Br, C_6H_5S and $C_6H_5SO_2$ in position 5 of the furan ring were determined at 25, 35 and 45°C (Table II). The values of velocity constants served for calculation of parameters E_a, ΔH^*, ΔS^*, and ΔG^*. The replacement of bromine was found to proceed most easily, ahd the rate constant k_2 of this reaction is higher when compared with that of the S_N reaction of 5-bromo--2-furfurylidenemalononitrile ($k_2 = 2{\cdot}063 \cdot 10^{-2}$ l mol^{-1} s^{-1}, Table III, ref.[4]) thus indicating a certain lowering of electron density in position 5 of the furan ring due to the bromine atom in position 4. The rate constant for 5-phenylthio-2-furfurylidenemalononitrile is, similarly, a little lower than that of the analogous 4-bromo-5(phenylthio derivative (derivative No 5, Table II). Derivatives No 3 and 6 (Table III) revealed approximately equal values. This fact might result from the bulkiness of the phenylsulfonyl grouping.

Kinetic investigation of bromine replacement in positions 2 and 5 of 2,3-dibromothiophene has already been reported[6]; these authors found k_2, 20°C = $0{\cdot}765 \cdot 10^{-4}$ l mol^{-1} s^{-1} in the reaction of the afore-mentioned compound with piperidine, what documented when compared with k_2, 20°C = $0{\cdot}175 \cdot 20^{-4}$ l mol^{-1} s^{-1} as determined by extrapolation in our determination for reaction of 4,5-dibromo-2--furfurylidenemalononitrile with piperidine, an enhanced effect of the nitro group attached to the thiophene ring in position 5 upon the rate of S_N reaction. The rate of S_N reaction of 4-bromo-5-X-2-furfurylidenemalononitriles with piperidine decreased in the series Br > C_6H_5S > $C_6H_5SO_2$, whilst 5-X-2-furfurylidenemalononitriles had the consecution changed to Br > $C_6H_5SO_2$ > C_6H_5S.

EXPERIMENTAL

The electron absorption spectra of methanolic solutions were measured with a Specord UV VIS (Zeiss, Jena) spectrophotometer at a $2-8 \cdot 10^{-5}$ mol l^{-1} concentration in 1 cm-cells; the measurement accuracy was ±1 nm. The IR spectra (KBr technique) recorded with a UR 20 (Zeiss,

Jena) apparatus were accurate to ± 2 cm^{-1}. The kinetics was measured at 25, 35 and 45 $\pm$ 0·2°C in the region of the absorption maximum of the product of the nucleophilic replacement. The reaction mixture consisted of 0·1—0·5 ml of the respective condensation product and 9·5—9·9 ml of the methanolic piperidine solution. The final concentration of the substrate in mixture was $1-5 \cdot 10^{-5}$ mol l^{-1}, and that of nucleophilic reagent $5 \cdot 10^{-2}$ mol l^{-1}. The apparent rate constants k_1(s^{-1}) were calculated from the linear relationship log $\Delta E = f(t)$, the second order rate constants k_2(1 mol^{-1} s^{-1}) were obtained from the slope of linear dependence of k' upon concentration of the nucleophile. The activation parameter values were calculated from the Arrhenius or Eyring dependences.

TABLE II

Rate constants k_2(1 mol^{-1} s^{-1}) and thermodynamic parameters of reaction of 2-cyano-3-(4--bromo-5-phenyl-X-2-furyl)-2-propenenitriles and methyl 2-cyano-3-(4-bromo-5-phenyl-X-2-furyl)-2-propenoates with piperidine in methanol

Compound	$k_2 \cdot 10^2$			E_a^a	ΔH^*	ΔS^*	ΔG^*
	25°	35°	45°				
Ia	18·21	20·32	22·50	31·21	28·75	223·65	95·39
Ib	2·62	4·27	5·72	29·94	27·48	233·96	97·20
IIj	2·62	4·33	7·54	41·64	39·18	232·52	108·47
IIe	1·09	1·95	3·22	42·54	40·08	239·09	111·32
IIf	3·25	5·06	6·80	30·85	28·42	233·18	97·90
IIa	1·17	2·15	2·86	35·12	32·56	239·09	103·90

[a] E_a in kJ mol^{-1}; ΔH^* in kJ mol^{-1}; ΔS^* in J grad^{-1} mol^{-1}; ΔG^* in kJ mol^{-1}.

TABLE III

Rate constants k_2(1 mol^{-1} s^{-1}) of reaction of 5-Y- and 4-X-5-Y-2-furfurylidenemalononitriles with piperidine in methanol at 25 $\pm$ 0·2°C

No	X	Y	$k_2 \cdot 10^2$
1	H	Br	2·06[a]
2	H	C_6H_5S	0·30[b]
3	H	$C_6H_5SO_2$	1·14[b]
4	Br	Br	18·21
5	Br	C_6H_5S	3·25
6	Br	$C_6H_5SO_2$	2·62

[a] Value from ref.[4]; [b] value from ref.[5].

2-Cyano-3-(4-bromo-5-R-X-2-furyl)-2-propenenitriles *Ia*, *IIf*—*IIj* and 2-Cyano-3-(4-bromo--5-R-X-2-furyl)-2-propenoates *Ib*, *IIa*—*IIe*

A) A solution of malononitrile (0·66 g, 10 mmol) or methyl cyanoacetate (1 g, 10 mmol) in ethanol (10 ml) was added to the aldehyde (10 mmol) dissolved in ethanol (20 ml). To the stirred solution 5 drops of 10% sodium ethanolate were added and after 1—2 h-stirring the separated compound was suction-filtered and dried. The filtrate, diluted with water, gave a further crop of the product. The combined compound was purified by crystallization from a proper solvent.

B) 2-Cyano-3-(4,5-dibromo-2-furyl)-2-propenenitrile or methyl 2-cyano-3-(4,5-dibromo-2--furyl)-2-propenoate (10 mmol) and sodium thiolate (10 mmol) were heated on a steam bath with stirring for 3—6, charcoal was added the mixture was simmered, filtered and the solvent was removed. The residue was crystallized from a suitable solvent. Physicochemical and analytical data of these compounds are listed in Table I.

Bis(3-bromo-5-formyl-2,2′-formyl) Sulfide (*IIIa*) and Bis(5-formyl-2,2′-furyl) Sulfide (*IIIb*)

4-X-5-Bromo-2-furaldehyde (10 mmol, X = H, Br) and $Na_2S.9\,H_2O$ (10 mmol) in water (10 ml) were stirred at 30—40°C untill a dark solution was formed. To this solution dimethyl sulfoxide (10 ml) was added and stirring was continued for 15 min at the same temperature; finally, 4-X-bromo-2-furaldehyde (10 mmol) in dimethyl sulfoxide was added and the mixture was stirred for additional 60 min, cooled to room temperature and water was added (100 ml). The separated compound was filtered off and crystallized from dilute ethanol.

Bis(3-bromo-5-formyl-2,2′-furyl) Selenide (*IVa*) and Bis(3-formyl-2,2′-furyl) Selenide (*IVb*)

A solution of $NaBH_4$ (0·3 g) in water (5 ml) was added under nitrogen to a stirred suspension of selenium (0·3 g) in water (5 ml). The mixture became foaming and after 10 min an almost colourless solution resulted to which 4-X-5-bromo-2-furaldehyde (3·9 mmol, X = H, Br) was given and the mixture was stirred at 40°C till dissolved. Dimethyl sulfoxide (5 ml) and after a 15 min--stirring another portion of 4-X-5-bromo-2-furaldehyde (3·9 mmol) in dimethyl sulfoxide (15 ml) were added, the mixture was stirred at 40—50°C for 30 min, cooled and poured into 50—100 ml of cold water. The crystals were filtered off, washed with water, dried and crystallized from n-heptane.

2-Cyano-3-(4-bromo-5-amino-2-furyl)-2-propenenitrile (*V*)

Powdered sodium azide (0·4 g, 60 mmol) was poured into a solution of 4,5-dibromo-2-furaldehyde (1·25 g, 5 mmol) in dimethyl sulfoxide (5 ml). The sodium azide being dissolved, a solution of malononitrile (1 g, 15 mmol) in ethanol (10 ml) was added. The mixture turned red and nitrogen began to evolve. The mixture was poured into cold water (200 ml) after the evolution of nitrogen ceased, the separated compound was filtered off and crystallized from ethanol.

Methyl 2-cyano-3-(4-bromo-5-amino-2-furyl)-2-propenoate (*VI*)

Sodium azide (0·4 g, 6 mmol) was added to a solution of methyl 2-cyano-3-(4,5-dibromo-2-furyl)--2-propenoate (1 g, 3 mmol) in dimethyl sulfoxide (5 ml) at 25°Cand the mixture was stirred until a red solution was formed. Malononitrile (0·4 g, 6 mmol) in ethanol (5 ml) was added, this stage being accompanied by an evaluation of nitrogen. The mixture was poured into water (100 ml) after 15 min and then it was left to stand. The separated compound was suction-filtered and crystallized form ethanol.

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