SYNTHESIS, REACTIONS AND SPECTRAL PROPERTIES OF ETHYL ESTERS OF 2-CYANO-3-(5-X-2-FURYL)ACRYLIC ACID

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Dedicated to Professor J. Kuthan on the occasion of his 60th birthday.

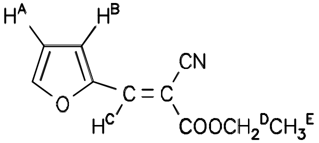
The reaction of 5-X-2-furaldehydes (X = C_6H_5, $COOCH_3$, $COOC_2H_5$, C_6H_5O, C_6H_5S, CH_3S, 4-Cl-C_6H_4S, CH_3SO_2, $C_6H_5SO_2$, 4-Cl-$C_6H_4SO_2$) with ethyl cyanoacetate in dry ethanol catalyzed by sodium ethoxide yielded the corresponding ethyl 2-cyano-3-(5-X-2-furyl)acrylates. It was found that the reactions of these esters with cyanoacetophenone or ethyl acetoacetate do not afford the corresponding 4*H*-pyran derivatives but that there proceeds the exchange of ethyl acetoacetate or of ethyl cyanoacetate for the cyanoacetophenone carbanion. The same course has been observed also for the reactions of these substrates with malononitrile.

Within the framework of the study of furylethylene derivatives, we were interested in condensation reactions of substituted 2-furaldehydes with malononitrile[1,2], methyl cyanoacetate[3], ethyl malonate[4], ethyl acetoacetate[4], phenylsulfonylacetonitrile and benzoylacetonitrile[5], and furylacetonitrile[6]. We have found that 2-cyano-3-(5-phenylsulfonyl-2-furyl)acrylate reported in one of our previous works[3] undergoes nucleophilic substitution in position 5 of the furan ring under mild reaction conditions, which leads to the preparation of some methyl analogues of the derivatives reported in the present work, e.g. substances *Il* – *In*. Kinetic study showed that the reaction rate of the condensation depends on the strength of the C–H acid[7].

In the present work we deal with the synthesis of ethyl esters of 2-cyano-3-(5-X-2-furyl)acrylic acid by reaction of 5-X-2-furaldehydes with ethyl cyanoacetate, using conditions of the Knoevelage reaction, in dry ethanol with added sodium ethoxide as a catalyst. These conditions made it possible to obtain the condensation products in about 80% yields, except for sulfones *Ih*, *Ii*, and *Ij* which were obtained in about 50% yields.

Therefore, the latter compounds were prepared in high yields by oxidation of sulfides *Ie*, *If*, and *Ig* by hydrogen peroxide in glacial acetic acid.

Physicochemical constants and elemental analyses of the prepared compounds *I* are presented in Table I.



I

	X		X
a	C_6H_5	*h*	CH_3SO_2
b	$COOCH_3$	*i*	$C_6H_5SO_2$
c	$COOC_2H_5$	*j*	$4-Cl-C_6H_4SO_2$
d	C_6H_5O	*k*	NH_2
e	CH_3S	*l*	1-pyrolidinyl
f	C_6H_5S	*m*	1-piperidinyl
g	$4-Cl-C_6H_4S$	*n*	1-morpholinyl

Compounds *Il*, *Im*, and *In* were synthesized by nucleophilic substitution of the readily leaving groups of the derivatives *Ie* – *Ii*. The latter substrates reacted with the corresponding secondary heterocyclic amines (pyrrolidine, piperidine, and morpholine) in several minutes under ambient temperature to give practically quantitative yields of the mentioned products. Under these conditions, the fastest reaction was observed for pyrrolidine, in harmony with the findings reported earlier[3].

The reaction of compounds *Ie* – *Ii* with ammonium formate in ethanol at a mildly elevated temperature for 1 h gives ethyl ester of 2-cyano-3-(5-amino-2-furyl)acrylic acid (*Ik*) in 48% yield. This reaction is the first example of the direct introduction of the amino group to furylethylene derivatives under very mild conditions.

The reaction of *In* with cyanoacetophenone in dry ethanol catalyzed by morpholine (to exclude the nucleophilic substitution in position 5 of the furan ring) did not yield the expected 2-amino-3-ethoxycarbonyl-4-(5-morpholino-2-furyl)-5-cyano-6-phenyl-4*H*-pyran, but there proceeded the replacement of ethyl cyanoacetate by the carbanion of cyanoacetophenone, affording the substance *II*. A similar situation has also been found for the reactions of the above substrates with ethyl acetoacetate which again did not give the 4*H*-pyran derivatives. The reactions of this type which involve nucleophilic exchange of the carbanions of C–H acids were studied by several authors[8 – 12].

TABLE I
Physicochemical constants of prepared compounds

Compound	Formula (M.w.)	M.p.^{a}, °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
Ia	$C_{18}H_{13}NO_3$	117 – 119	71.90	4.90	5.24	–
	(267.3)	72	72.24	4.99	5.09	
Ib	$C_{12}H_{11}NO_5$	125 – 126	57.83	4.45	5.62	–
	(249.2)	89	57.51	4.23	5.48	
Ic	$C_{13}H_{13}NO_5$	95 – 96	59.31	4.98	5.32	–
	(263.2)	87	59.02	4.78	5.01	
Id	$C_{18}H_{13}NO_4$	89 – 90	67.84	4.63	4.94	–
	(283.3)	70	68.07	4.74	4.83	
Ie	$C_{11}H_{11}NO_3S$	81 – 83	55.68	4.67	5.90	13.5
	(237.3)	69	55.44	4.56	6.19	14.14
If	$C_{18}H_{13}NO_3S$	100 – 102	64.20	4.38	4.68	10.71
	(299.3)	73	64.44	4.48	4.23	11.06
Ig	$C_{18}H_{12}ClNO_3S$	81 – 82	57.57	3.62	4.20	9.61
	(333.8)	82	58.00	4.06	3.88	9.31
Ih	$C_{11}H_{11}NO_5S$	133 – 136	49.06	4.12	5.20	11.91
	(269.3)	85	49.18	4.18	4.99	11.97
Ii	$C_{18}H_{13}NO_5S$	139 – 142	58.00	3.95	4.23	9.68
	(331.3)	83	57.88	4.32	3.76	9.22
Ij	$C_{18}H_{12}ClNO_5S$	128 – 131	52.54	3.31	3.83	8.77
	(365.8)	86	52.01	3.87	3.61	8.85
Ik	$C_{10}H_{10}N_2O_3$	154 – 156	58.25	4.89	13.59	–
	(206.2)	48	58.14	4.83	13.43	
Il	$C_{14}H_{18}N_2O_3$	135 – 136	65.60	6.20	10.76	–
	(260.3)	86	65.44	6.58	10.69	
Im	$C_{15}H_{18}N_2O_3$	131 – 133	65.68	6.61	10.21	–
	(274.3)	85	66.12	7.03	10.62	
In	$C_{14}H_{18}N_2O_4$	125 – 127	60.86	5.84	10.14	–
	(276.3)	82	61.25	6.16	9.90	
IIa	$C_{19}H_{18}N_4O_4$	290 – 295	62.63	4.43	15.38	–
	(364.3)	81	63.06	4.68	14.82	

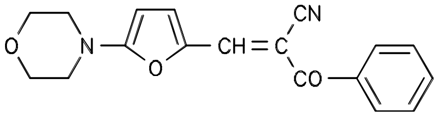
TABLE I
(*Continued*)

Compound	Formula (M.w.)	M.p.[a], °C Yield, %	Calculated/Found			
			% C	% H	% N	% S
IIb	$C_{15}H_{14}N_4O_8$	253 – 256	52.02	4.07	16.18	–
	(346.3)	69	52.35	4.20	15.69	
IIc	$C_{18}H_{18}N_4O_8$	227 – 229	53.33	4.48	15.55	–
	(360.3)	67	53.11	4.23	15.12	
III	$C_{18}H_{16}N_2O_3$	178 – 180	70.12	5.23	9.09	–
	(308.3)	37	69.82	4.78	8.94	

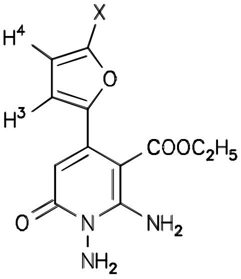
[a] Crystallized from ethanol.

These studies have shown that the leaving group is the weaker C–H acid, as the same effects that increase the acidity of the hydrogens (especially an electron-acceptor effect of substituents) aid also in the resonance stabilization of the alkene, which shifts the equilibrium toward formation of the more stable product.

Similar results were obtained by us also in the reactions of substrates *I* with malononitrile in 5% ethanolic sodium ethoxide solutions. Neither in this case the expected 2-pyridone derivative was formed, the product being that of the nucleophilic replacement of ethyl cyanoacetate by the carbanion of malononitrile.



III



II

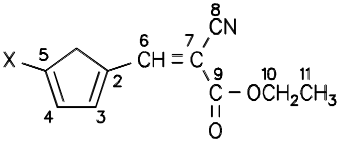
	X
a	C_6H_5
b	$COOCH_3$
c	$COOC_2H_5$

2-Pyridone derivatives *IIIa* – *IIIc* were prepared by the reactions of substrates *Ia* – *Ie* (taken to eliminate the S_N reaction in position 5 of the furan) with the hydrazide of cyanoacetic acid in dry ethanol catalyzed by sodium ethoxide. The reactions were carried out at ambient temperature, with intense stirring of the reaction mixture for 2 h.

The IR spectra of compounds *Ia* – *In* (Table II) show characteristic bands of the cyano group in the 2 210 – 2 230 cm^{-1} region. Also symmetric (1 010 – 1 030 cm^{-1}) and antisymmetric (1 230 – 1 260 cm^{-1}) ν(C–O–C) bond vibrations are well observable. The stretching ν(C=C) bond vibrations occur in the 1 500 – 1 700 cm^{-1} region. The IR spectra of 2-pyridones *IIIa* – *IIIc* show in addition to ν(C=O) vibrations of the ester group at 1 720 cm^{-1} also absorption maxima at around 1 650 cm^{-1}, which proves that the studied *N*-amino-2-pyridones are in the lactame tautomeric form. This is evidenced also by the absence of absorption bands belonging to the hydroxyl group. These conclusions agree well with the results reported by Otta and coworkers[13]. The spectra of 1-amino-2-pyridones show also absorption bands corresponding to symmetric (3 310 – 3 220 cm^{-1}) and antisymmetric (3 390 – 3 400 cm^{-1}) NH_2 group vibrations.

The study of ^1H NMR spectra of compounds *Ia* – *In* (Table III) has shown that the change of the substituent in position 5 of the furan ring affects markedly the chemical shift of hydrogen in position 4, while that of the hydrogen in position 3 is much less affected. In the spectra of 1-amino-2-pyridones one observes the distinct singlets of the amino groups. The amino group attached to the nitrogen shows the singlet in the 5.72 ppm region while that attached to the carbon has the singlet in the 8.53 ppm region.

The interaction constants ^3J(C–H) (12 – 13 Hz) obtained by ^{13}C NMR spectroscopy of substances *Ia* – *Ij* demonstrate unambiguously that these compounds are the E isomers. The chemical shifts of the carbons of ^{13}C derivatives *Ia* – *Ij* are presented in Table IV . The numbering of the carbons is shown in Scheme 1.



SCHEME 1

EXPERIMENTAL

UV absorption spectra were measured on M-40 Zeiss Jena spectrophotometer, using 20 mm cells and 10^{-4} M solutions of substances in dry ethanol. IR spectra were measured on PU 9800 Phillips instrument, using KBr discs. ^1H NMR spectra of compounds *Ia* – *In* were measured in $CDCl_3$ and those of compounds *IIa* – *IIc* in $(CD_3)_2SO$ (BS 487 C Tesla instrument working at 100 MHz), using tetramethylsilane as an internal reference. ^{13}C NMR spectra of compounds *Ia* – *Ij* were measured in $CDCl_3$ on Varian XL-300 spectrometer, using tetramethylsilane as an internal reference.

TABLE II
IR spectra of ethyl esters of 2-cyano-3-(5-X-2-furyl)acrylic acid (in cm^{-1})

Compound	ν(CN)	ν(C=O)	ν(C=C)	ν_s(C–O–C)	ν_{as}(C–O–C)
Ia	2 218	1 709	1 611	1 032	1 233
Ib	2 228	1 714	1 618	1 019	1 250
Ic	2 226	1 717	1 617	1 013	1 240
Id	2 218	1 709	1 617	1 022	1 240
Ie	2 218	1 711	1 607	1 024	1 242
If	2 220	1 725	1 605	1 019	1 246
Ig	2 220	1 709	1 603	1 020	1 246
Ih	2 226	1 715	1 624	1 017	1 258
Ii	2 234	1 736	1 615	1 019	1 254
Ij	2 230	1 732	1 615	1 013	1 250
Ik	2 210	1 668	1 611	1 030	1 250
Il	2 199	1 662	1 584	1 028	1 254
Im	2 197	1 672	1 591	1 022	1 256
In	2 237	1 718	1 602	1 024	1 249

TABLE III
^{1}H NMR spectra of ethyl esters of 2-cyano-3-(5-X-2-furyl)acrylic acid

Compound	δH_A	δH_B	δH_C	δH_D	δH_E
Ia	6.91	arom[a]	7.97	4.37	1.39
Ib	7.32	7.60	8.12	4.38	1.39
Ic	7.31	7.61	8.13	4.38	1.39
Id	5.62	arom[a]	7.85	4.34	1.37
Ie	6.44	7.27	7.85	4.35	1.37
If	6.61	arom[a]	7.93	4.35	1.37
Ig	6.66	arom[a]	7.91	4.35	1.37
Ih	7.48	7.30	8.06	4.39	1.40
Ii	arom[a]	arom[a]	arom[a]	4.36	1.37
Ij	arom[a]	arom[a]	arom[a]	4.37	1.38
Ik	5.65	7.58	7.43	4.18	1.26
Il	5.77	7.56	7.41	4.16	1.23
Im	5.76	7.56	7.42	4.16	1.23
In	5.47	7.53	7.52	4.29	1.35

[a] Signal is overlapped with multiplet of hydrogens of the aromatic ring. [b] Signal of NH_2 group at $\delta = 8.21$ ppm.

Synthesis of Compounds *Ia* – *Ig*

5-X-2-Furaldehyde (0.02 mol) was dissolved in 20 – 50 ml of dry ethanol (the volume depended on the solubility of a given aldehyde) with mild heating. Then, freshly redistilled ethyl cyanoacetate (2.2 g; 0.02 mol) and 1 drop of 5% solution of ethanolic sodium ethoxide were added. The reaction mixture was allowed to stand at −10 °C to 0 °C for 24 h. Then the precipitated condensate was separated by filtration with suction, followed by recrystallization from ethanol.

Synthesis of Compounds *Ih* – *Ij*

Substances *Ie* – *Ig* (0.005 mol) were dissolved in 100 ml of glacial acetic acid at mildly elevated temperature, and then 3 ml of 30% hydrogen peroxide solution were added. The solution was allowed to stand at ambient temperature for 3 days , then it was condensed to the half volume by vacuum evaporation and 60 ml of ice water were added. After 2 h, the precipitated sulfone was filtered off with suction and recrystallized from ethanol.

Synthesis of Compound *Ik*

Ethyl ester of 2-cyano-3-(5-methylthio-2-furyl)acrylic acid (2.37 g; 0.01 mol) was dissolved at 50 °C in 20 ml of dry ethanol. Then, ammonium formate (0.95 g; 0.015 mol) was added and the reaction mixture was stirred at 40 – 50 °C for l h. After cooling the reaction mixture to −10 °C, the precipitate so formed was filtered off with suction, washed with distilled water and recrystallized from ethanol.

TABLE IV
^{13}C NMR spectra of prepared compounds *Ia* – *Ij* (in ppm)

Compound	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}
Ia	147.69	129.71	108.90	159.80	138.01	96.92	115.75	162.92	62.27	14.11
Ib	147.40	120.21	119.70	150.63	139.23	102.96	114.55	161.48	62.92	14.05
Ic	147.73	120.20	119.47	150.51	139.26	102.79	114.47	161.49	62.86	14.03
Id	140.54	126.01	91.09	162.95	138.24	94.23	115.80	162.95	62.10	14.10
Ie	149.53	124.69	112.09	158.19	137.42	95.87	115.79	163.05	62.28	14.18
If	150.50	122.76	117.59	154.48	138.24	97.44	115.16	162.95	62.41	14.07
Ig	150.73	122.67	118.01	152.89	138.09	98.62	115.07	162.30	62.49	14.05
Ih	152.86	119.80	118.26	151.30	138.29	104.41	114.24	161.17	63.20	14.06
Ii	153.58	120.21	118.25	151.49	134.47	103.76	114.12	161.19	62.98	13.95
Ij	153.17	120.18	118.35	151.63	137.87	104.03	114.08	161.14	63.05	13.96

[a] For numbering of carbons see Scheme 1.

TABLE V
Spectral characteristics of compounds *IIa* – *IIc*

Type of spectrum	Compound		
	IIa	*IIb*	*IIc*
IR spectrum, cm^{-1}			
$\nu(C\equiv N)$	2 209	2 215	2 220
$\nu(C=O)$	1 720	1 719	1 719
$\nu(C=C)$	1 613	1 601	1 603
$\nu(C=O)$, lactam.	1 654	1 651	1 655
$\nu_s(C-O-C)$	1 007	1 013	1 013
$\nu_{as}(NH_2)$	3 395	3 393	3 393
$\nu_s(NH_2)$	3 311	3 320	3 309
UV spectrum, λ_{max}, nm/log ε			
	202	203	204
	[a]	3.32	3.34
	271	272	272
	[a]	3.38	3.40
	300	304	305
	[a]	3.05	3.08
	364	355	356
	[a]	3.18	3.20
^1H NMR, δ ppm			
furan ring			
H_3'	6.96	6.97	6.99
H_4'	7.46	7.49	7.45
ester group			
$-CH_2-$	4.21	3.34	3.89
$-CH_3$	1.22	0.86	0.91
amino groups			
$N-NH_2$	5.73	5.71	5.72
$C-NH_2$	8.53	8.53	8.53

[a] Saturated solution in methanol.

Synthesis of Compounds *IIa* – *IIc*

Compounds *Ia* – *Ic* were dissolved in 30 ml of dry ethanol, and then hydrazide of cyanoacetic acid (1 g; 0.01 mol) and sodium ethoxide (1 g) were added. The reaction mixture was stirred at ambient temperature for 3 h. Then, the precipitate formed was filtered off with suction and recrystallized from ethanol. Spectral characteristics are given in Table V.

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