REACTIONS OF 1-CYANO-1-R-2-(5-X-2-FURYL)ETHYLENES WITH NUCLEOPHILIC REAGENTS*

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The Knoevenagel condensation of phenylsulphonylacetonitrile and benzoylacetonitrile with 5-X-furane-2-carbaldehydes (X = Br, NO_2, C_6H_5S, $C_6H_5SO_2$) has been used for preparation of the respective condensation products 1-cyano-1-fenylsulphonyl-2-(5-X-2-furyl)- and 1-cyano-1-benzoyl-2-(5-X-2-furyl)ethylenes. These condensation products react with nucleophilic reagents which replace the group X at the 5 position of the furane nucleus. These nucleophilic substitutions have been also studied kinetically.

From the available data on the nucleophilic substitution of phenylsulphonyl group at the 5 position of furane nucleus it follows that the S_N reaction only takes place if there is a strong electron-acceptor group at the 2 position of the furane ring. Such reactions proceed very easily with 5-phenylsulphonyl-2-furfurylidenemalonnitrile[1] and methyl 5-phenylsulphonyl-2-furfurylidenecyanoacetate[2]. On the contrary, the substitution of phenylsulphonyl group in 5-phenylsulphonylfurane-2-carbaldehyde does not take place even under drastic reaction conditions, due to insufficient electron--acceptor effect of the aldehydic group.

The present communication deals with the preparation of a series of 1-cyano--1-phenylsulphonyl-2-(5-X-2-furyl)- $(Ia-Id)$ and 1-cyano-1-benzoyl-2-(5-X-2-furyl)-ethylenes $(Ie-Ih)$ and with their reactions with nitrogen-containing nucleophilic reagents: piperidine, pyrrolidine, morpholine, N-phenylpiperazine $(IIa-IIh)$. The said 1,1,2-trisubstituted ethylenes were prepared by the reaction of 5-X-furane--2-carbaldehydes with phenylsulphonylacetonitrile or benzoylacetonitrile under the conditions of the Knoevenagel condensation in high yields. The nucleophilic substitution reactions of these substrates with the above-mentioned nucleophilic reagents proceed easily to give the respective 5-amino derivatives. The reactions were carried out, first of all, in methanol and ethanol, in some cases it was advantageous to use dimethyl sulphoxide or dimethylformamide. Structure of the compounds prepared was proved by elemental analysis, UV and ${}^1H$ NMR spectra (Table I).

TABLE I

Physico-chemical data of the compounds prepared

Compound	Formula (m.w.)	M.p., °C yield, %	Calculated/Found				λ_{max}, nm log ε			^{1}H NMR (δ, ppm; J, Hz)				
			% C	% H	% N	% S				m, 5 H C_6H_5	d, 1 H H_A	d, 1 H H_B	s, 1 H H_C	J_{AB}
Ia	$C_{13}H_8BrNO_3S$ (338·1)	157^a 87	46·13 46·05	2·36 2·21	4·14 4·10	9·48 9·32	210 3·11	235 2·86	355 3·50	7·45—8·13	6·61	7·26	7·36	2·4
Ib	$C_{13}H_8N_2O_5S$ (304·2)	186^b 85	51·27 51·22	2·62 2·39	9·21 9·18	10·53 10·48	209 3·05	248 3·07	354 3·36	7·57—8·1	7·46	7·99	7·72	2·5
Ic	$C_{19}H_{13}NO_3S_2$ (367·4)	84^a 69	62·00 61·92	3·53 3·50	3·81 3·78	17·45 17·34	212 3·22	240 3·05	398 3·25	7·05—8·07	6·51	7·24	7·27	4·6
Id	$C_{19}H_{13}NO_5S_2$ (399·4)	159^a 76	57·08 56·98	3·25 3·17	3·51 3·50	16·05 14·98	210 3·18	238 3·15	340 3·40	7·42—8·17	7·24	7·28	7·95	1·8
Ie	$C_{14}H_8BrNO_2$ (302·1)	132^a 80	55·61 55·59	2·64 2·57	4·63 4·58	—	210 3·30	260 3·02	368 3·50	7·67—8·01	6·63	7·53	7·87	2·8
If	$C_{14}H_8N_2O_4$ (268·2)	156^b 75	62·63 62·57	2·98 2·77	10·45 10·31	—	210 3·16	234 3·13	356 3·30	7·7—8·03	7·52	7·88	7·62	2·5
Ig	$C_{20}H_{13}NO_2S$ (331·3)	73^a 80	72·42 72·29	3·92 3·87	4·23 4·18	9·67 9·59	212 3·25	—	400 3·19	7·6—7·97	6·62	7·35	7·49	3·5
Ih	$C_{20}H_{13}NO_4S$ (363·3)	127^a 83	66·04 65·98	3·57 3·52	3·86 3·78	8·82 8·65	211 3·31	231 3·22	343 3·36	7·75—7·98	7·34	7·48	7·84	3·6

Compound	Formula (M)	M.p. (°C) / Yield (%)	Calc./Found C	H	N	(extra)									
IIa	C$_{18}$H$_{18}$N$_2$O$_3$S (342·3)	139^c / 75	63·09 / 62·96	5·25 / 5·21	8·18 / 8·07	9·34 / 9·25	208 / 3·08	233 / 3·13	338 / 2·87	467 / 3·72	7·5–8·07	5·49	7·11	7·35	3·5
IIb	C$_{17}$H$_{16}$H$_2$O$_3$S (328·3)	90^c / 68	62·13 / 61·95	4·87 / 4·69	8·53 / 8·42	9·74 / 9·67	227 / 3·02	285 / 2·71	357 / 2·77	470 / 3·25	7·67–8·07	6·32	7·54	7·3	4·5
IIc	C$_{17}$H$_{16}$N$_2$O$_4$S (344·3)	149^d / 62	59·24 / 59·10	4·64 / 4·51	8·14 / 8·15	9·29 / 9·11	230 / 3·10	273 / 2·67	—	464 / 3·56	7·65–8·1	5·52	7·16	7·58	3·5
IId	C$_{23}$H$_{21}$N$_3$O$_3$S (419·4)	137^b / 59	65·80 / 65·21	5·01 / 4·92	10·02 / 9·97	7·63 / 7·61	208 / 3·01	240 / 2·91	343 / 2·82	455 / 2·90	7·52–8·04	5·74	7·23	7·49	3·1
IIe	C$_{19}$H$_{18}$N$_2$O$_2$ (306·3)	117^a / 58	74·42 / 74·31	5·87 / 5·59	9·14 / 9·07	—	208 / 4·08	238 / 2·93	285 / 2·52	500 / 3·62	7·37–7·97	5·59	7·18	7·51	4·2
IIf	C$_{18}$H$_{16}$N$_2$O$_2$ (292·3)	165^b / 72	73·88 / 73·80	5·47 / 5·39	9·58 / 9·42	—	208 / 3·10	238 / 2·93	283 / 2·52	515 / 3·61	7·37–7·95	5·49	7·17	7·25	3·5
IIg	C$_{18}$H$_{16}$N$_2$O$_3$ (308·3)	149^c / 69	70·05 / 69·95	5·18 / 5·04	9·08 / 9·12	—	210 / 3·21	238 / 3·04	280 / 2·65	500 / 3·71	7·37–7·97	5·59	7·40	7·50	3·9
IIh	C$_{24}$H$_{21}$N$_3$O$_2$ (383·4)	225^d / 80	75·11 / 74·97	5·47 / 5·37	10·96 / 10·84	—	210 / 3·39	243 / 3·27	280 / 2·69	500 / 3·84	7·37–7·92	5·63	6·92	7·25	3·0

^{a} Ethanol; ^{b} chloroform; ^{c} methanol; ^{d} ether.

The electronic absorption spectra of the two series of condensation products show the absorption maxima in the regions 209−212 nm, 231−260 nm, and 340 to 400 nm. The absorption bands at the lower wavelengths correspond to the $\pi \rightarrow \pi^*$


I   *II*
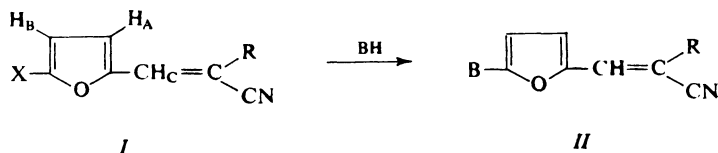
Ia, X = Br; R = $C_6H_5SO_2$	*IIa*, B = PI; R = $C_6H_5SO_2$
Ib, X = NO_2; R = $C_6H_5SO_2$	*IIb*, B = PY; R = $C_6H_5SO_2$
Ic, X = C_6H_5S; R = $C_6H_5SO_2$	*IIc*, B = MO; R = $C_6H_5SO_2$
Id, X = $C_6H_5SO_2$; R = $C_6H_5SO_2$	*IId*, B = FP; R = $C_6H_5SO_2$
Ie, X = Br; R = C_6H_5CO	*IIe*, B = PI; R = C_6H_5CO
If, X = NO_2; R = C_6H_5CO	*IIf*, B = PY; R = C_6H_5CO
Ig, X = C_6H_5S; R = C_6H_5CO	*IIh*, B = MO; R = C_6H_5CO
Ih, X = $C_6H_5SO_2$; R = C_6H_5CO	*IIh*, B = FP; R = C_6H_5CO

BH = piperidine(PI), pyrrolidine(PY), morpholine(MO), N-phenylpiperazine(FP).

and $n \rightarrow \pi^*$ electronic transitions of benzene and furane, and the longest-wave band is due to the oscillations of the π electrons in the whole conjugated system (K-band). The X substituents affect distinctly the K-band, *e.g.* that of the 5-phenylthio derivatives extends into visible region. The spectra of the products of the nucleophilic substitutions show 4 absorption maxima, the last absorption band being found in the visible region. This result is due to the replacement of phenylsulphonyl group at the 5 position of furane ring by the nitrogen-containing functional group with a free electron pair at the nitrogen atom which enables formation of strongly polar quinoid structures, whence also the intensive colour of these compounds can be explained (Scheme 1).
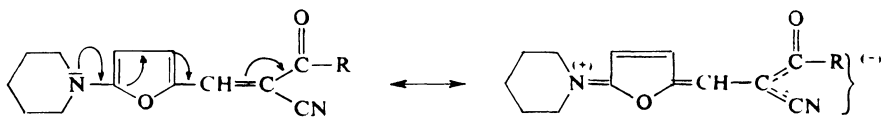
SCHEME 1

Furthermore, kinetics of the nucleophilic substitution reaction of 1-cyano-1-phenyl-sulphonyl- or -1-benzoyl-2-(5-X-2-furyl)ethylenes with the nitrogen-containing nucleophilic reagents (pyrrolidine, piperidine, morpholine, and N-phenylpiperazine) was followed with respect to the effects of the nucleophile, substituent at the 5 position of the furane nucleus, and solvent. All the reactions studied were realized under the

conditions of a pseudomonomolecular reaction with excess nucleophilic reagent. The reaction was found to be first order in the substrate and first order in the nucleophilic reagent. The apparent rate constants k' were calculated from the dependence $\log(a - x) = f(t)$, and the constants k_2 from the equation $k' = k_{solv} + k_2[$nucleophile$]$, the values k_{solv} being substantially lower than k_2. The effect of the nucleophilic reagent on the course of the S_N reaction can be seen from the k_2 values given in Table II. In the both series of the substrates studied the rate constants increase with increasing nucleophilicity of the reagent. As the slowest reaction step consists in the attack of the furane 5 position by the nucleophile (analogous results were obtained in the series of 5-substituted 2-furfurylidenemalonnitriles, too[1]), the highest k_2 value is — according to what was expected — that of the reaction with pyrrolidine (the nucleophilicity 5·67), followed by almost equal value of N-phenylpiperazine (5·59) and piperidine (5·59), and the slowest reaction is that with morpholine[3,4] (5·29). Approximately the same order was obtained also when the reactions were carried out in methanol (Table II).

The effect of the 5-X substituent in the furane nucleus on the rate of the S_N reaction was followed in a series of 1-cyano-1-phenylsulphonyl-(5-X-2-furyl)ethylenes with

TABLE II

Rate constants k_2 (l mol^{-1} s^{-1}) of S_N reactions of 1-cyano-1-R-2-(5-X-2-furyl)ethylenes with nucleophilic reagents in dimethylformamide or methanol at $25 \pm 0.2°C$

No	X	R	Reagent[a]	Dimethylformamide		Methanol	
				λ_{max}, nm	$k_2 . 10^3$	λ_{max}, nm	$k_2 . 10^3$
1	$C_6H_5SO_2$	$C_6H_5SO_2$	PY	520	14·5	468	5·32
2	$C_6H_5SO_2$	$C_6H_5SO_2$	PI	517	12·1	465	2·12
3	$C_6H_5SO_2$	$C_6H_5SO_2$	FP	517	6·12	453	4·83
4	$C_6H_5SO_2$	$C_6H_5SO_2$	MO	520	1·88	468	1·38
5	$C_6H_5SO_2$	C_6H_5CO	PY	500	3·21	—	
6	$C_6H_5SO_2$	C_6H_5CO	PI	465	3·28	—	
7	$C_6H_5SO_2$	C_6H_5CO	FP	487	3·17	—	
8	$C_6H_5SO_2$	C_6H_5CO	MO	487	2·12	—	
9	Br	$C_6H_5SO_2$	PI	453	31·6	468	2·11
10	NO_2	$C_6H_5SO_2$	PI	457	32·3	460	13·05
11	C_6H_5S	$C_6H_5SO_2$	PI	465	10·6	468	1·64
12	Br	C_6H_5CO	PI	487	5·32	—	
13	NO_2	C_6H_5CO	PI	unmeasurable, complex		—	
14	C_6H_5S	C_6H_5CO	PI	500	1·85	—	

[a] The symbols are explained in the formulas given.

X = Br, NO$_2$, C$_6$H$_5$S, C$_6$H$_5$SO$_2$ (Table II, the derivatives 2, 9, 10, 11). The highest k_2 value was found for NO$_2$ group (Table II, derivative 10), and the decreasing order is NO$_2$ > Br > C$_6$H$_5$SO$_2$ > C$_6$H$_5$S. From the comparison of k_2 of the substitution of the bromo and nitro derivatives it can be seen that the k_2 value is lower for Br which is connected with a greater repulsive force to the nucleophilic reagent. In the case of the phenylsulphonyl group (a soft base) as the leaving group it is obvious that the main effect on the lowering of reactivity of the phenylsulphonyl derivatives (as compared with nitro or bromo derivatives) is that of the bulkiness of phenyl group and its sterical interaction with the nucleophilic reagents. The lowest rate constants were found with the thiophenolate group in which the free electron pair of the sulphur atom participates in the conjugation with the furane nucleus, whereby the electron deficit at C$_{(5)}$ of furane is decreased.

The abovementioned S$_N$ reactions were also studied with respect to solvent effects, *viz.* in N,N-dimethylformamide and in methanol. For all the 5-substituted derivatives (X = Br, NO$_2$, C$_6$H$_5$SO$_2$, C$_6$H$_5$S) of the two series, the rate constants are higher in dimethylformamide than in methanol (with all the secondary amines used).

Comparison of the two series (R = phenylsulphonyl or benzoyl group) shows that the k_2 values are higher for the phenylsulphonyl group in all the cases (Table II).

EXPERIMENTAL

The electronic absorption spectra were measured in the region of 200—600 nm using a recording spectrophotometer Specord UV VIS. The measurements were carried out in methanol in 1 cm cells at the concentrations 3 . 10^{-5} to 7 . 10^{-5} mol l^{-1} with the accuracy of ±1 nm. The ^{1}H NMR spectra were measured at 80 MHz with a Tesla BS 487 C spectrometer in hexadeuteriodimethyl sulphoxide using tetramethylsilane as the internal standard.

Preparation of 1-Cyano-1-phenylsulphonyl-2-(5-X-2-furyl)
and 1-Cyano-1-benzoyl-2-(5-X-2-furyl)ethylenes

A mixture of 0·01 mol phenylsulphonylacetonitrile or benzoylacetonitrile, 0·01 mol 5-X-furane--2-carbaldehyde (X = Br, NO$_2$, C$_6$H$_5$S, C$_6$H$_5$SO$_2$), catalytic amount of sodium methoxide, and 50—70 ml methanol was stirred and heated at 40°C 2—3 h. After the reaction was finished, the mixture was poured onto 100 g crushed ice. The separated solid was collected by suction, dried, and recrystallized from a suitable solvent (Table I).

Reactions of 1-Phenylsulphonyl-1-cyano-2-(5-phenylsulphonyl-2-furyl)ethylene *(Id)*
with Nucleophilic Reagents

A solution of 0·001 mol *Id* in 20—30 ml ethanol was heated to boiling. Then, 0·0015 mol nucleophilic reagent (piperidine, pyrrolidine, morpholine, N-phenylpiperazine) was added, and the mixture was heated with stirring 3—6 h. The reactions with piperidine and morpholine gave solid products which were collected by suction and recrystallized (Table I). In the case of other derivatives the reaction mixture was evaporated, and the residue was submitted to column chromatography (alumina; chloroform–methanol 10 : 3). It is advantageous to use dimethyl

sulphoxide as the solvent in the reactions with pyrrolidine and N-phenylpiperazine: after the reaction was finished, the mixture was poured into water, extracted with ether, the ether extract was concentrated and treated further in usual way.

Reactions of 1-Cyano-1-benzoyl-2-(5-phenylsulphonyl-2-furyl)ethylene (*Ih*) with Nucleophilic Reagents

A solution of 0·001 mol *Ih* in 20 ml ethanol was heated to boiling, and 0·0015 mol nucleophilic reagent was added thereto portionwise. The mixture was heated with stirring 2—6 h. After the reaction was finished, the mixture was treated in the same way as above. It is advantageous to use dimethylformamide as the solvent in the reaction with piperidine. The results are given in Table I.

Kinetic Measurements

The kinetic measurements were carried out with a Specord UV VIS spectrophotometer in 1 cm tempered cells at the wavelength of the absorption maximum of the product formed by the nucleophilic substitution. These analytical wavelengths (visible region) are given in Table II.

The kinetics of the S_N reaction was measured in a reaction mixture consisting of 0·3—0·7 ml 1-cyano-1-phenylsulphonyl-2-(5-X-2-furyl)ethylene in the respective solvent and 0·3—9·9 ml of the respective solution of nucleophilic reagent. The starting concentrations of the substrate and the nucleophile were $(3—7) . 10^{-5}$ mol l^{-1} and $1 . 10^{-1}$ mol l^{-1}, respectively. The apparent rate constants k' were calculated from the slope of the dependence $\log(a - x) = f(t)$ and were divided by the nucleophilic reagent concentration to give the rate constants k_2. The results of the kinetic measurements are given in Table II.

REFERENCES

1. Kada R., Knoppová V., Kováč J.: Syn. Commun. *7*, 157 (1977).
2. Kada R., Knoppová V., Kováč J., Večeřa Z.: This Journal *45*, 1831 (1980).
3. Hall H. K.: J. Org. Chem. *29*, 3539 (1964).
4. Popov A. F., Kostanko L. I., Kravčenko V. V., Végh D., Kováč J.: *Topics in Chemistry of Heterocyclic Compounds*, p. 261. The Edition Centre of Slovak Technical Institute, Bratislava 1981.

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