

KINETICS OF NUCLEOPHILIC REPLACEMENT OF 2,5-DISUBSTITUTED FURANS*

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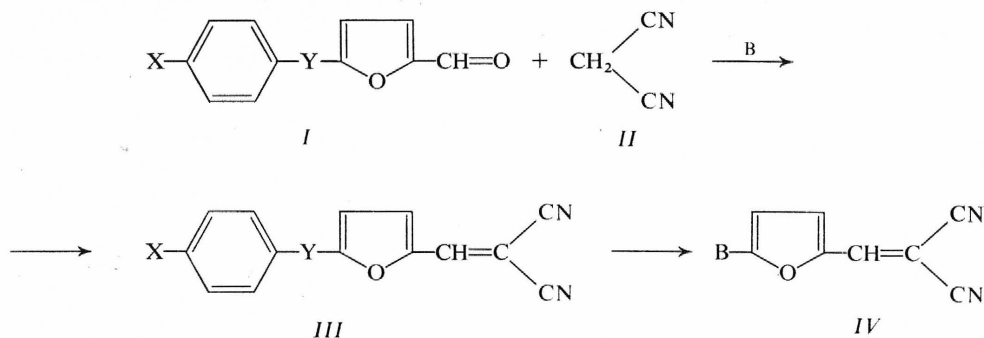
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The kinetics of nucleophilic substitution reaction of 5-(4-X-phenylthio- (A), and 4-X-phenylsulphonyl)-2-furfurylidene malononitriles (B) ($X = H, Cl, Br, CH_3CONH, CH_3O, CH_3, NO_2$ for series A, and $X = H, Cl, Br, CH_3CONH, N(CH_3)_2, CH_3, CH_3O$ for series B) with secondary cyclic amines was studied. The effect of the substituent X in position 4 of the aromatic ring on the rate of the S_N reaction, on the transmission of polar effects of the substituent through phenylthio and phenylsulphonyl groups, and also influencing this reaction by the nature of the nucleophilic reagent were investigated. Thermodynamic parameters of this reaction were determined.

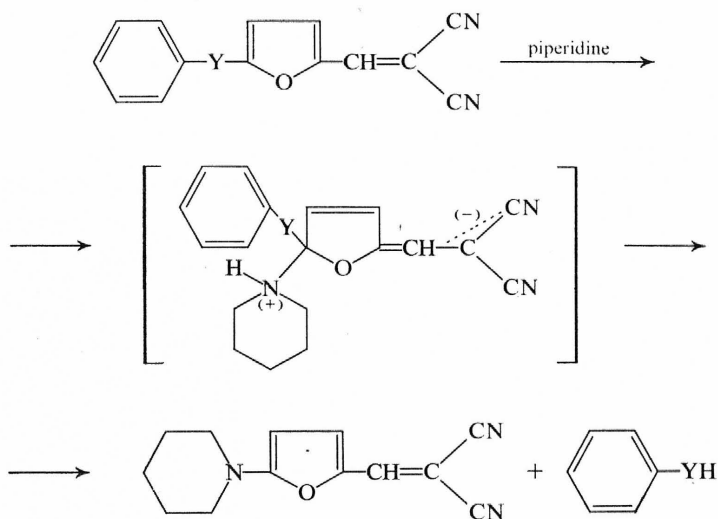
As we reported¹, the Knoevenagel condensation of 5-arylthio- and 5-arylsulphonyl-2-furaldehydes (I) with malonitrile (II) led, in the presence of secondary cyclic amines (piperidine, morpholine, etc.) to the formation of a normal product of condensation III in the first step, i.e. to the corresponding derivative of acrylonitrile, and in the next step an S_N replacement of arylthio- or arylsulphonyl group to yield the appropriate 5-amino derivative IV took place.

This paper deals with the study of kinetics in the last step of the reaction, i.e. with the nucleophilic replacement at which besides of piperidine and morpholine also pyrrolidine and N-phenylpiperazine were used as nucleophilic reagents. The reaction with piperidine was studied in detail with derivatives III (Scheme 1), where $X = H, Cl, Br, CH_3CONH, CH_3O, CH_3, NO_2$ and $Y = S$, and alternatively $X = H, Cl, Br, CH_3CONH, N(CH_3)_2, CH_3, CH_3O$ and $Y = SO_2$; the reaction with morpholine was studied only with derivative III, $X = H, Y = SO_2$. Reactions carried out in methanolic medium under conditions of pseudomonomolecular reaction and excess of nucleophilic reagent were monitored by spectrophotometric method. Relationship of the apparent rate constants k' upon concentration of nucleophilic reagent was found to be linear; consequently, the reaction is of first order in respect to the nucleophile. The rate constants k_2 for equation $v = k_2 \cdot [dinitrile] \cdot [piperidine]$ were calculated from the linear relationship k' on the concentration of the nucleophile employing

* Part CXIX in the series Furan Derivatives; Part CXVIII: This Journal 43, 3252 (1978).



Y = S, SO₂ B = piperidine, morfoline



SCHEME 1

equation $k' = k_{\text{solv}} + k_2 \cdot [\text{piperidine}]$, where the rate constants of solvolysis are lower than k_2 . The measured rate constants of the S_N reaction with piperidine are listed in Table I for both series. The rate constants k_2 of the 4-X-phenylsulphone derivatives are higher than those of the sulphide series. The relationship $\log k_2$ on Hammett σ_p constants of substituents is linear with $\rho = 0.293$, $r = 0.99$ ($n = 7$) for the sulphide series and $\rho = 0.231$, $r = 0.92$ ($n = 7$) for the sulphone series (Fig. 1). As seen, the reaction rate depends on the magnitude of the electron deficiency at position 5 of the furan ring; the electron-donating substituents were found to lower, electron-withdrawing ones to rise the rate of substitution. The low ρ values for both series indicate the magnitude of the electron density at position 5 of the furan ring

to be influenced mainly by the electron-withdrawing $-\text{CH}=\text{C}(\text{CN})_2$ group and to a less extent also by the substituted phenylthio and phenylsulphonyl groups. The ratio $k_{\text{SO}_2}/k_{\text{S}} = 3.13$ (for $\text{X} = \text{H}$) evidences the greater deactivation of position 5 of the furan ring by phenylsulphonyl group than by the phenylsulphidic one.

The influence of the nucleophilicity of various secondary amines on the course of S_{N} reaction was investigated with the fundamental phenylsulphonyl derivative III, $\text{X} = \text{H}$, $\text{Y} = \text{SO}_2$ under like condition as with reaction with piperidine. Morpholine, N-phenylpiperazine and pyrrolidine were the secondary amines used in this reaction.

TABLE I

Kinetic Data of the S_{N} Reaction of 2-Cyano-(5-(4-X-phenyl-Y)-2-furyl)acrylonitrile with Piperidine in Methanol at $t = 25 \pm 0.2^\circ\text{C}$

No	X	Y	$k' \cdot 10^3$ s^{-1}	$k_2 \cdot 10^3$ $\text{l mol}^{-1} \text{s}^{-1}$	$t_{1/2}$ s	$3 + \log k_2$
1	H	S	0.150	3.00	4 613.3	0.4771
2	Cl	S	0.182	3.64	3 802.1	0.4611
3	Br	S	0.189	3.78	3 661.3	0.5774
4	CH_3CONH	S	0.146	2.97	4 739.7	0.4653
5	CH_3O	S	0.1267	2.53	5 461.7	0.4031
6	CH_3	S	0.140	2.80	4 942.8	0.4471
7	NO_2	S	0.254	5.08	2 724.4	0.7058
8	H	SO_2	0.470	11.36	1 472.3	1.0553
9	Cl	SO_2	0.649	12.98	1 086.2	1.1132
10	Br	SO_2	0.628	12.56	1 101.9	1.0989
11	CH_3CONH	SO_2	0.502	10.94	1 378.4	1.0017
12	$\text{N}(\text{CH}_3)_2$	SO_2	0.381	7.62	1 816.2	0.8819
13	CH_3	SO_2	0.450	9.00	1 537.7	0.9542
14	CH_3O	SO_2	0.400	8.00	1 730.0	0.9031

FIG. 1

Relationship Between the Rate Constants of S_{N} Reaction with Piperidine in Methanol and Hammett σ_{p} Constants of Substituents of Both Series of Derivatives at $25 \pm 0.2^\circ$ (lettering of derivatives according to Table I)

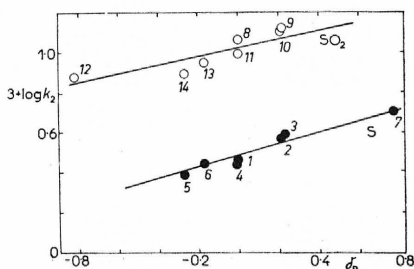


TABLE II
Kinetic and Thermodynamic Parameters of S_N Reaction of 2-Cyano-3-(5-phenylsulphonyl-2-furyl)acrylonitrile with Nucleophiles in Methanol at Various Temperatures

Nu- cleoph. reag. M/l · 10 ²	18°C ^a			25°C ^a			35°C ^a			E_a^a	ΔH^{**a}	ΔS^{**a}
	$k \cdot 10^3$	$k_2 \cdot 10^3$	$t_{1/2}$	$k' \cdot 10^3$	$k_2 \cdot 10^3$	$t_{1/2}$	$k' \cdot 10^3$	$k_2 \cdot 10^3$	$t_{1/2}$			
Piperidine												
2	0.1329	8.47	5 206.9	0.129	11.36	5 364.3	0.357	20.46	1 938.3	9.35	8.94	-37.44
4	0.301		2 299.0	0.331		2 090.6	0.760		910.5			
5	0.387		1 788.1	0.470		1 472.3	0.971		712.6			
Morpholine												
2	0.0313	2.86	22 108.6	0.0433	4.24	15 981.5	0.074	5.80	9 351.3	7.64	7.04	-45.75
4	0.090		7 688.8	0.147		4 707.4	0.180		3 844.4			
5	0.117		5 914.5	0.1705		4 058.6	0.248		2 790.3			
N-Phenylpiperazine												
2	0.0672	5.63	10 297.6	0.0756	9.146	9 153.4	0.096	13.46	7 208.3	9.41	8.82	-38.28
4	0.190		3 642.1	0.260		2 661.5	0.345		005.7			
5	0.238		2 907.5	0.350		1 977.1	0.500		592.0			
Pyrrolidine												
2	0.442	9.93	1 565.2	0.566	16.13	1 222.6	1.000	24.00	692.0	9.53	8.94	-36.74
4	0.665		1 040.7	0.816		848.0	1.47		470.7			
5	0.770		898.7	1.050		659.0	1.72		402.3			

^a k given in s^{-1} ; k_2 l/mol · s; $t_{1/2}$ s; E_a kcal/mol; ΔH^* kcal/mol; $\Delta S^* = eu$.

The obtained kinetic parameters and thermodynamic values are listed in Table II. As seen, the rate of nucleophilic replacement is proportional to the increasing nucleophilicity of the reagent. Pyrrolidine was estimated to react most easily, the rate then decreases in the order: piperidine, N-phenylpiperazine and morpholine.

Basing both upon our results and analogous reactions in the thiophene series² one is entitled to presume an addition-elimination mechanism of this reaction in which the reaction determining step is the attack of the nucleophilic reagent to the substrate.

EXPERIMENTAL

5-(4-X-Phenylthio)-2-furaldehydes employed in these experiments were prepared by reacting the respective thiophenolates with 5-bromo-2-furaldehyde in ethanol, or acetone³, 5-(4-X-phenylsulphonyl)-2-furaldehydes were synthesized from 5-bromo-2-furaldehyde with alkali salts of benzenesulphonic acids⁴. Their condensation products with malonodinitrile were prepared according to⁵. Preparation and physicochemical properties of 5-piperidino-, 5-morpholino-, 5-pyrrolidino- and 5-N-phenylpiperazino- derivatives are given in¹. All substances were purified either by crystallization or distillation prior to kinetic measurements.

Kinetic Measurements

Registration spectrophotometer UV VIS (Zeiss) was employed for kinetic measurements in the range of absorption maximum of the derivative under formation *IV* at 18, 25 and 35°C ± 0.2°C. The reaction mixture consisted of a 0.1–0.5 ml ethanolic solution of *III* and 9.5–9.9 ml of the methanolic solution of the respective secondary amine. The final concentrations of the substrate in the mixture and the nucleophilic reagent were 1–5 · 10⁻⁵ and 5 · 10⁻²M, respectively. The apparent rate constants *k'* (s⁻¹) were calculated from the line slope of the linear dependence log Δ*E* = *f*(*t*) by the least squares method. Second order rate constants *k*₂ (l mol⁻¹ s⁻¹) were calculated from the line slope of the linear relationship *k'* on the concentration of the nucleophilic reagent. Activation energy was calculated from Arrhenius equation, the variations of activation entropy and enthalpy at 25°C were obtained in a usual manner.

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