

Furan derivatives

CC. Study of the reactions of 2-X-3-(5-Y-2-furyl- and -2-thienyl)-acrylonitriles with 4-aminopyridine

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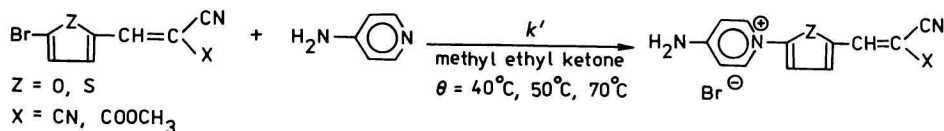
Received 19 September 1983

Kinetics of the reaction of 2-X-3-(5-bromo-2-furyl- and -2-thienyl)acrylonitriles (where X = CN, COOCH₃) with 4-aminopyridine and pyridine has been studied in methyl ethyl ketone at 40 °C, 50 °C, and 70 °C. The reactivity is compared with respect to nucleophilicity of the reagent, nature of the electron-withdrawing group in the position 2 of the heterocyclic ring, and to the nature of the 5-membered heterocycle. When running these reactions in DMFA, DMSO, and HMPT, a donor-acceptor complex was formed due to interaction of the substrate with the solvent. The time dependence of formation of these complexes is discussed.

Изучена кинетика реакций 2-X-3-(5-бром-2-фурил- и 2-тиенил)акрилонитрилов (где X = CN, COOCH₃) с 4-аминопиридином и пиридином в метилэтилкетоне при 40 °C, 50 °C и 70 °C. Сопоставлены реакционные способности в зависимости от нуклеофильности реагента, природы электроноакцепторной группы в положении 2 гетероцикла и природы 5-членного гетероцикла. При проведении этих реакций в ДМФ, ДМСО и ГМФТ образовывался донорно-акцепторный комплекс вследствие взаимодействия субстрата с растворителем. Обсуждается временная зависимость образования этих комплексов.

It has been recognized that substitution nucleophilic reactions on furan ring proceed under rather hard reaction conditions only when the group to be replaced is a halogen atom or a nitro group [1—3]. Therefore, majority of the reactions studied so far concern those derivatives which have a further electron-withdrawing group in their molecules [4—8]. The halogen in 5-halo-2-nitrofurans enters the S_N reactions most readily [9, 10]. In this connection, nucleophilic substitution reactions were studied with furan derivatives having phenylthio [11, 12], phenylsulfonyl [13, 14], methylthio [15], methylsulfonyl [15], and substituted phenoxy groups [16] bound in the position 5, while in the position 2 strong electron-withdrawing groups (—CH = C(CN)₂ or —CH = C(CN)COOCH₃) were present.

S_N reactions of the above-mentioned furan and thiophene derivatives with pyridine and its derivatives have not been studied so far. The present paper deals with investigation of kinetics of the reaction of 3-substituted 2-cyanoacrylonitriles of the furan and thiophene series with 4-aminopyridine according to Scheme 1.



Scheme 1

The kinetics of the S_N reaction was followed under pseudounimolecular reaction conditions at three temperatures using excess amount of the nucleophilic reagent, *i.e.* 4-aminopyridine. Graphical evaluation as well as calculations revealed a first-order reaction with respect to both the starting compound and the nucleophilic reagent.

As evident from the rate constants in Table 1, the rate of this reaction depends on the electron-withdrawing properties of the substituent in the position 2 of the heterocycle and on the type of the 5-membered heterocycle.

Since the rate-determining step of the reaction is the attack of the nucleophilic reagent, the rate of the S_N reaction will be influenced also by the nucleophilicity of the reagent. Accordingly, we obtained measurable rate constants with 4-aminopyridine, while with pyridine the reaction proceeded very slowly for several days under the same conditions. This fact follows from comparison of the $pK(b)$ values for 4-aminopyridine (4.89) and pyridine (8.98).

Table 1

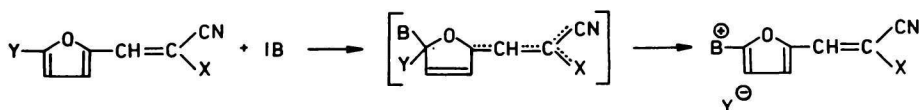
Numerical values of rate constants $k_2/(dm^3 mol^{-1} s^{-1})$ for the reaction of 2-X-3-(5-bromo-2-furyl)- and -(5-bromo-2-thienyl)acrylonitriles with 4-aminopyridine in methyl ethyl ketone at $\theta = (70.0 \pm 0.2)^\circ C$

Heteroaryl	X	$\{k\} \cdot 10^2$		$t_{1(2)}/s$	
		1	2	1	2
Furyl	CN	4.90	7.91	2829	1753
Furyl	COOCH ₃	1.77	4.26	7801	3250
Thienyl	CN	1.20	—	11498	—

1 — Maximum of the absorption band belonging to the starting compound ($\lambda \approx 360$ nm);
 2 — maximum of the absorption band belonging to the product ($\lambda \approx 470$ nm).

The kinetics of the nucleophilic replacement was followed by decrease of the absorption maximum of the starting compound ($\lambda \approx 360$ nm) as well as by increase of the absorption band of the product ($\lambda \approx 470$ nm). As seen from Table 1, these values differ, which indicates that the S_N reaction is not a one-step reaction. After the first attack by the nucleophilic reagent, representing the rate-determining step of the reaction, several rapid steps follow to give the final product on splitting off of Y. The reaction proceeds at highly negative ΔS^* value (Table 2, Scheme 2).

The S_N reactions in the position 5 of the furan and thiophene rings are facilitated by strong electron-withdrawing groups in the position 2. The rate constants (Table 1) are higher with condensation products containing $-\text{CH}=\text{C}(\text{CN})_2$ group than with those with $-\text{CH}=\text{C}(\text{CN})\text{COOCH}_3$ group as a consequence of higher positive fractional charge on the C-5 carbon atom of the 5-membered heterocycle in the case of the dinitrile group.



Scheme 2

Table 2

Thermodynamic quantities for the reaction of 2-cyano-3-(5-bromo-2-furyl)acrylonitrile with 4-aminopyridine in methyl ethyl ketone at $\theta = 40^\circ\text{C}$, 50°C , and 70°C

$\lambda_{\text{max}}/\text{nm}$	$\log \{k_2\}$ 40 °C	$\log \{k_2\}$ 50 °C	$\log \{k_2\}$ 70 °C	E_A	ΔH^*	$-\Delta S^*$	ΔG^*
				kJ mol^{-1}	kJ mol^{-1}	$\text{J mol}^{-1} \text{K}^{-1}$	kJ mol^{-1}
358	-1.71	-1.56	-1.31	26.8	24.2	164.8	102.0
448	-1.37	-1.26	-1.10	18.9	14.7	188.4	100.1

The S_N reaction proceeding directly on the heterocyclic ring is affected to a considerable degree also by the nature of the heterocycle. The presence of oxygen as the heteroatom in furan, reluctant to delocalize its lone electron pair to electrodeficient carbon C-5, is the reason of higher reactivity of furan derivatives when compared to thiophene derivatives containing sulfur as the heteroatom.

Since it is known that S_N reactions proceed readily in strongly polar solvents, we endeavoured to carry out the reactions mentioned above in DMFA as a polar

solvent. We have found, however, that on dissolving the respective acrylonitrile in DMFA the UV spectrum changed and a new band appeared in the region of $\lambda \approx 470$ nm. Strongly electron-withdrawing and electron-donating systems interact with the solvent forming electron-donor-acceptor (EDA) complexes. Their formation is connected with charge transfer and characterized by occurrence of a new absorption band in the electronic spectra [17]. In our case, acrylonitrile acted as the electron-acceptor and DMFA as the electron-donor (Scheme 3).



Scheme 3

We have found that the complex is not formed immediately but its concentration increases with time. From the course of the kinetic curve we calculated the first-order reaction rate constants for the complex formation in dependence on temperature (Table 3). At 25 °C the rate constant with 5-nitro-2-furyl derivative was 38 times higher than that with 5-bromo-2-furyl derivative (Table 4) due to better charge distribution in the case of the nitro group.

Table 3

Numerical values of rate constants k_1/s^{-1} for the formation of the complex of 2-cyano-3-(5-bromo-2-furyl)acrylonitrile in DMFA at $\theta = 25$ °C, 35 °C, and 45 °C and in DMSO and HMPT at $\theta = 25$ °C

Solvent	$\{k_1\} \cdot 10^4$ 25 °C	$\{k_1\} \cdot 10^4$ 35 °C	$\{k_1\} \cdot 10^4$ 45 °C
DMFA	1.287	2.244	3.562
DMSO	0.672	—	—
HMPT	0.374	—	—

Table 4

Numerical values of rate constants k_1/s^{-1} for the formation of the complex of 2-cyano-3-(5-bromo- and -5-nitro-2-furyl)acrylonitrile in DMFA at $\theta = (25.0 \pm 0.2)$ °C

Derivative	$\{k_1\} \cdot 10^4$	λ_{\max}/nm
5-Bromo-	0.883	360
5-Nitro-	30.44	363

The time progress of the complex formation in dependence on the temperature is linear ($\log \{k\}$ vs. $1/T$) and fulfils the Arrhenius relationship. Similar results were obtained also by monitoring the changes in the UV spectrum in DMSO and HMPT. The rate of the complex formation (Table 3) decreased with the increasing relative permittivity of the solvent ($\epsilon_r(\text{DMFA}) = 36.7$; $\epsilon_r(\text{DMSO}) = 48.1$).

Experimental

2-Cyano-3-(5-bromo-2-furyl)acrylonitrile, 2-cyano-3-(5-bromo-2-thienyl)acrylonitrile, methyl 2-cyano-3-(5-bromo-2-furyl)acrylate, and 2-cyano-3-(5-nitro-2-furyl)acrylonitrile were prepared as model compounds. The preparation of the respective pyridinium salts is described in [18].

The kinetics of the substitution nucleophilic reaction was monitored spectrophotometrically [11] on a UV VIS Specord spectrophotometer (Zeiss, Jena) in 1 cm cells tempered at 40–70 °C at the wavelengths of the absorption maxima of both the starting compound and the product using methyl ethyl ketone as solvent. At the end of the reaction the UV spectrum of the reaction mixture was measured. This spectrum was identical with those of the corresponding pyridinium salts prepared synthetically.

Kinetics was followed in the reaction mixture containing 0.01 M solution of the respective condensation product (0.05 cm³; its resulting concentration in the mixture was 5×10^{-5} mol dm⁻³), 0.1 M solution of the nucleophilic reagent (0.5 cm³; its resulting concentration in the mixture was 5×10^{-3} mol dm⁻³), and methyl ethyl ketone (9.45 cm³). Measurements were carried out against the same mixture without the respective condensation product. The reaction was run at conditions of a pseudomolecular reaction. The apparent rate constants k' were calculated from the slope of the relationship $\log \{a - x\} = f(t)$ and by dividing these values with concentration of the nucleophilic reagent in the mixture, the rate constants k_2 in dm³ mol⁻¹ s⁻¹ were obtained.

The kinetics of the donor-acceptor complex formation in DMSO, DMFA, and HMPT was monitored spectrophotometrically at 25–45 °C by the band belonging to the complex in the visible region of the UV spectrum. The resulting concentration of acrylonitriles in the reaction mixture was 5×10^{-5} mol dm⁻³.

References

1. Manly, D. G. and Amstutz, E. D., *J. Org. Chem.* 21, 516 (1956).
2. Gronowitz, S. and Sörlin, G., *Acta Chem. Scand.* 15, 1419 (1961).
3. Schweizer, E. E. and Light, K. K., *J. Org. Chem.* 31, 870 (1966).
4. Nazarova, Z. N., *Zh. Obshch. Khim.* 25, 539 (1955).
5. Nazarova, Z. N., *Zh. Obshch. Khim.* 27, 2931 (1957).
6. Nazarova, Z. N. and Garnovskii, A. D., *Zh. Obshch. Khim.* 30, 1182 (1960).
7. Nazarova, Z. N. and Gakh, I. G., *Zh. Obshch. Khim.* 30, 2322 (1960).
8. Novikov, V. N., *Khim. Geterotsikl. Soedin.* 1976, 1601.

9. Novikov, V. N. and Nazarova, Z. N., *Zh. Org. Khim.* 1, 2022 (1965).
10. Shigetaka Yoshina, Motoi Aoki, Kasuke Ito, and Masanu Miyake, *Yakugaku Zasshi* 91, 467 (1971).
11. Knoppová, V., Kada, R., and Kováč, J., *Collect. Czech. Chem. Commun.* 43, 3409 (1978).
12. Kada, R., Knoppová, V. and Kováč, J., *Collect. Czech. Chem. Commun.* 42, 3333 (1977).
13. Kada, R., Knoppová, V., Kováč, J., and Balag, M., *Collect. Czech. Chem. Commun.* 45, 2360 (1980).
14. Kada, R., Knoppová, V., Kováč, J., and Večeřa, Z., *Collect. Czech. Chem. Commun.* 45, 1831 (1980).
15. Knoppová, V., Kada, R., and Kováč, J., *Chem. Zvesti* 34, 556 (1981).
16. Knoppová, V., Dandárová, M., and Kováč, J., *Collect. Czech. Chem. Commun.* 46, 506 (1981).
17. *Reaktive Zwischenstufen in der organischen Chemie*, p. 23. Akademie-Verlag, Berlin, 1981.
18. Kríž, M. and Kováč, J., *Collect. Czech. Chem. Commun.*, in press.

Translated by A. Kardošová