THE REACTION OF METHYL 2-CYANO-3-(5-PHENYLSULPHONYL-2-FURYL)ACRYLATE WITH NUCLEOPHILES*

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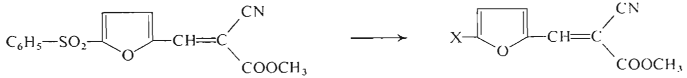
In suitable solvents, methyl 2-cyano-3-(5-phenylsulphonyl-2-furyl)-acrylate reacts with nucleophiles, *e.g.* piperidine, pyrrolidine, morpholine, N-phenylpiperazine, N-methylpiperazine, N-benzylpiperazine, hexamethyleneimine, dimethylamine, diethylamine and sodium azide, to afford products of nucleophilic substitution of the phenylsulphonyl group at the position 5 of the furan ring. The course of the nucleophilic substitution has been monitored kinetically.

We have previously described[1,2] a nucleophilic substitution of arylthio, heteroarylthio and arylsulphonyl groups in 2-cyano-3-(5-arylthio-2-furyl), 2-cyano-3-(5-heteroarylthio-2-furyl) and 2-cyano-3-(5-arylsulphonyl-2-furyl)acrylates with N-nucleophiles.

We have found now that a nucleophilic substitution of an arylsulphonyl group takes place (Scheme 1), and most easily with N-nucleophiles, also in methyl 2-cyano-



I

II

IIa, X = dimethylamino
IIb, X = diethylamino
IIc, X = pyrrolidino
IId, X = piperidino
IIe, X = morpholino
IIf, X = N-phenylpiperazino
IIg, X = N-benzylpiperazino
IIh, X = N-methylpiperazino
IIi, X = hexamethylenimino
IIj, X = azido
IIk, X = phenylthio

SCHEME 1

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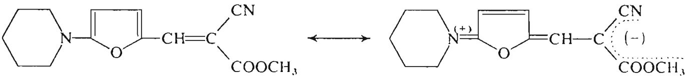
* Part CIL in the series Furan derivatives; Part CXLVIII: This Journal *45*, 1715 (1980).

-3-(5-phenylsulphonyl-2-furyl)acrylate (*I*). Compound *I* was obtained by Knoevenagel condensation of 5-phenylsulphonyl-2-furaldehyde with methyl cyanoacetate. In addition to comparing their physico-chemical properties, the structures of the products of the nucleophilic substitutions were confirmed by reactions of 5-X-2-furaldehydes with methyl cyanoacetate. The reaction products are coloured substances and their electron spectra show three absorption bands of which that beginning at the largest wave-length value stretches far into the visible region, as a result of the formation of highly polar structures (Scheme 2). The described S_N reaction is faciliated by the electron-withdrawing $CH{=}C(CN)COOCH_3$ substituent at the position 2 of the furan ring. This is strongly suggested by the fact that, in spite of drastic conditions applied, a similar substitution reaction with 5-phenylthio- and 5-phenylsulphonyl-2-furaldehydes was unsuccessful. The successful reactions were performed at ambient temperature with piperidine, pyrrolidine, dimethylamine and sodium azide, or at 50°C with N-phenylpiperazine, morpholine, hexamethyleneimine and diethylamine in sulpholane or tetrahydrofuran and comparable yields were obtained also in methanol. Interestingly, the yields of the desired products were by about 20% lower when dimethylformamide was used as a solvent. It appears that under these conditions a competitive reaction of the substrate with dimethylformamide takes place, the latter being able to act as either an N- or O-nucleophile. A similar phenomenon has been proved by kinetic measurements to occur in hexamethyl phosphoric acid triamide.



SCHEME 2

It follows from the results obtained that the described nucleophilic substitution reactions take place easily with N-nucleophiles. Reactions with S-nucleophiles occur in a similar way, which is demonstrated by the reaction of *I* with thiophenol (Table I, compound *IIk*). On the other hand, reactions under a variety of conditions with other nucleophiles, *e.g.* thiocyanates, sodium amide, nitriles, fluorides, alcoholates or phenolates, were unsuccessful.

We have studied also the kinetics of the described nucleophilic substitution on the furan ring. The experiments were performed under the conditions of pseudounimolecular reactions, *i.e.* using an excess of the nucleophilic reagent. It has been found that the nucleophilic substitution is a second order reaction, first order with respect to either of the reactants involved. It can be seen (Table II) that at 30°C in methanol the reaction rate is proportional to the increasing nucleophility of the reagent, *i.e.* carried out with various nucleophiles it increases in the order: pyrrolidine > piper idine > hexamethyleneimine > N-methylpiperazine > N-benzylpiperazine > N-phenylpiperazine > morpholine, confirming that the rate-determining step of the reaction is the attack of the nucleophile. In kinetic studies also analogous 5-phenylthio, 5-nitro and 5-bromo derivatives[3-5] have been used as standard materials. It is well known that the rate of an S_N2—Ar reaction largely depends upon the nature of the solvents. It follows from the data in Tables III and IV that the rate of the S_N reaction is highest in sulpholane and it decreases through that in dimethyl sulphoxide to that in methanol, in accord with the dielectric constant of these solvents. The order of

TABLE I

Methyl 2-Cyano-3-(5-X-furyl)acrylates

Compound	Molecular formula (m. w.)	M. p, °C (yield, %)	Calculated/Found			λ_{max}, nm (log ε)		
			% C	% H	% N			
IIa	$C_{11}H_{12}N_2O_3$ (220·2)	155–156 (87)	59·99 59·78	5·49 5·43	12·71 12·66	—	235 (3·46)	466 (4·86)
IIb	$C_{13}H_{16}N_2O_3$ (248·2)	103 (68)	62·89 62·74	6·49 6·44	11·28 11·23	—	237 (4·21)	464 (4·91)
IIc	$C_{13}H_{14}N_2O_3$ (242·2)	165 (92)	64·46 64·42	5·82 5·80	11·56 11·54	208 (3·75)	235 (4·13)	471 (4·74)
IId	$C_{14}H_{16}N_2O_3$ (256·2)	105 (87)	65·62 65·57	6·29 6·26	10·92 10·90	213 (4·14)	238 (4·43)	465 (5·04)
IIe	$C_{13}H_{14}N_2O_4$ (258·2)	136·5 (95)	60·46 60·28	5·46 5·39	10·84 10·80	211 (4·15)	237 (4·29)	462 (4·68)
IIf	$C_{19}H_{19}N_3O_3$ (333·3)	134·5 (82)	68·46 68·24	5·74 5·68	12·60 12·49	211 (4·39)	244 (4·42)	466 (4·79)
IIg	$C_{20}H_{21}N_3O_3$ (347·3)	67 (72)	69·15 68·94	8·56 8·42	12·09 11·98	211 (4·02)	234 (4·23)	463 (4·67)
IIh	$C_{14}H_{17}N_3O_3$ (271·2)	242 (54)	61·98 61·73	6·32 6·29	15·48 15·39	211 (3·92)	229 (4·57)	465 (4·93)
IIi	$C_{15}H_{18}N_2O_3$ (274·3)	124 (58)	65·68 65·60	6·61 6·57	10·21 10·51	209 (4·12)	238 (4·35)	470 (4·92)
IIj	$C_9H_6N_5O_3$ (218·1)	107 (67)	49·55 49·40	2·77 2·66	32·08 31·94	211 (3·96)	242 (4·14)	391 (4·23)
IIk	$C_{15}H_{11}NO_3S$ (285·3)	95–97 (74)	—	—	—	210 (4·22)	241[a] (4·00)	371 (4·33)

[a] Shoulder.

exchange of the substituents (NO_2, Br, C_6H_5S and $C_6H_5SO_2$) is the same in all the solvents studied and the S_N reaction is fastest with the nitro and slowest with the phenylsulpho derivative. Since the reaction of the phenylthio derivative in methanol

TABLE II

Rate Constants (k', s^{-1}, $t = 35 \pm 0{\cdot}2$ °C) for S_N Reactions of Methyl 2-Cyano-3-(5-phenylsulphonyl-2-furyl)acrylate with Various Nucleophiles in Methanol

Reagent	$k' \cdot 10^4$	Reagent	$k' \cdot 10^4$
Pyrrolidine	7·3	N-Phenylpiperazine	0·27
Piperidine	2·2	N-Benzylpiperazine	0·78
Hexamethyleneimine	4·7	N-Methylpiperazine	0·89
Morpholine	0·23		

TABLE III

Rate Constants ($k' \cdot 10^4$, s^{-1}, $t = 35 \pm 0{\cdot}2$°C) for S_N Reactions of Methyl 2-Cyano-3-(5-Y-2-furyl)acrylates with Piperidine under the Conditions of a Pseudounimolecular Reaction

Y	C_6H_5S	$C_6H_5SO_2$	Br	NO_2
Methanol	—	2·20	28·7	43·7
Dimethyl sulphoxide	1·83	3·56	35·6	87·5

TABLE IV

Rate Constants (s^{-1}) and Thermodynamical Parameters for Reactions of Methyl 2-Cyano-3-(5-Y-furyl)acrylates with Piperidine in Sulpholane

Y	$k' \cdot 10^4$			E_A kJ/mol	ΔH kJ/mol	$-\Delta S^*$ J . $grad^{-1}$ mol^{-1}	ΔG^* kJ/mol
	25°	35°	45°				
C_6H_5S	2·11	2·94	4·12	31·90	29·39	217·71	96·42
$C_6H_5SO_2$	3·72	11·2	24·5	72·55	70·00	75·79	93·32
NO_2	52·1	97·4	244·0	60·37	57·81	96·00	87·38
Br	24·1	44·1	99·2	55·14	52·58	119·74	89·47

at 35°C proceeds at a sufficiently slow rate its temperature-dependence in the range of 25 – 45°C was studied (Table IV) and the observed data have been used to calculate the thermodynamical parameters. The strongly negative $-\Delta S^*$ value is indicative of a highly polar intermediate formed in the first stage of the reaction[1].

EXPERIMENTAL

Methyl 2-Cyano-3-(5-phenylsulphonyl-2-furyl)acrylate (*I*)

Methyl cyanoacetate (0·02 mol) in ethanol (10 ml) followed by a catalytic amount of sodium ethoxide was added to a solution of 5-phenylsulphonyl-2-furaldehyde (0·02 mol) in ethanol (50 ml) and the mixture was stirred at ambient temperature for 3 h. The separated material was filtered, washed with cold ethanol, the filtrate was diluted with water, the precipitate was combined with the main portion of the product and recrystallization from ethanol gave yellow material in 75·5% yield, m.p. 117°C. For $C_{15}H_{11}NO_5S$ (317·3) calculated: 56·78% C, 3·47% H, 4·41% N, 10·09% S; found: 56·62% C, 3·45% H, 4·38% N, 10·01% S.

Methyl 2-Cyano-3-(5-X-2-furyl)acrylates (*IIa – IIk*)

A) A mixture of *I* (0·01 mol) and a nucleophile (0·01 mol) in sulpholane (50 ml) was stirred at ambient or slightly elevated temperature for 10 – 15 h. After addition of water (5 ml) the mixture was stirred for 30 min, poured into water (250 ml), the precipitate was filtered and recrystallized from ethanol. For preparation of methyl 2-cyano-3-(5-dimethylamino-2-furyl)acrylate gaseous dimethylamine was lead into the mixture until the weight-gain of the mixture corresponded to 0·01 mole. The reactions with piperidine, pyrrolidine, morpholine, N-phenylpiperazine, hexamethyleneimine and diethylamine were carried out as described above.

B) A mixture of methyl 2-cyano-3-(5-phenylsulphonyl-2-furyl)acrylate (0·01 mol), N-methyl- or N-benzylpiperazine (0·01 mol) and sodium carbonate (0·01 mol) in tetrahydrofuran (50 ml) was stirred at 50°C for 24 h. After concentration, the residue was dissolved in ethanol and ether was added until sodium benzenesulphinate started to precipitate. The mixture was filtered and the filtrate concentrated to give an oil which solidified when kept in a refrigerator for a longer period, and recrystallization from ethanol afforded pure products.

Methyl 2-Cyano-3-(5-azido-2-furyl)acrylates

A mixture of methyl 2-cyano-3-(5-phenylsulphonyl-2-furyl)-acrylate (0·001 mol) and sodium azide (0·002 mol) in sulpholane (5 ml) was stirred in the dark at room temperature for 5 h. The mixture was poured into cold water (20 ml) and the yellow-green, crystalline precipitate was recrystallized from ethanol (20 ml), with the exclusion of light.

Methyl 2-cyano-3-(5-bromo-2-furyl)-, 2-cyano-3-(5-nitro-2-furyl)- and 2-cyano-3-(5-phenylthio-2-furyl)acrylates were prepared as described[3–5].

Kinetic Measurements

The measurements for solutions in methanol and dimethyl sulphoxide at 25 – 45°C were performed using a UV-VIS (Zeiss) spectrometer and 1 cm cells. The amount of the formed substitution product, depending upon the nucleophile, was monitored by the band at ~467 nm

(Table I, third band). The kinetics of the reaction was studied with a reaction mixture consisting of 0·1—0·5 ml of the ester and 9·5—9·9 ml of a solution of the corresponding nucleophile. The final concentration of the substrate was $1-5 \, . \, 10^{-5}$M and that of the nucleophile was $\sim 5 \, . \, 10^{-2}$M. The apparent rate-constant k' was calculated from the tangency of the linear dependence, log $\Delta E - f(t)$. Activation energies were calculated according to the Arrhenius equation.

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