

CONDENSATIONS OF 5-HETEROARYLTHIO-2-FURALDEHYDES WITH C-ACIDS*

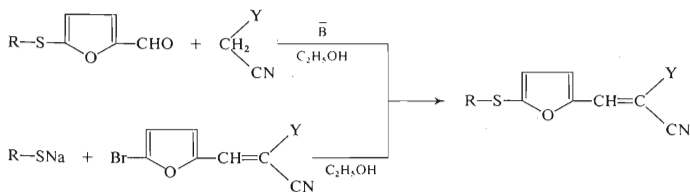
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Received January 20th, 1977

Reaction of 5-heteroarylthio-2-furaldehydes, where heteroaryl is 2-benzimidazolyl, 2-benzoxazolyl, 2-benzthiazolyl, 2-benzselenazolyl or 2-pyrimidinyl group, with malononitrile, methyl cyanoacetate, benzyl cyanide or 4-nitrobenzyl cyanide afforded corresponding acrylonitrile derivatives. Kinetic studies of these condensations were performed.

Within the framework of our study of sulphur-containing furan derivatives we described in our previous papers the preparation and properties of 5-arylthio- and 5-heteroarylthio-2-furaldehydes¹, as well as condensation reactions of 5-arylthio-2-furaldehydes with compounds containing active methylene groups^{2,3}. This paper concerns the Knoevenagel condensation of 5-heteroaryl-2-furaldehydes with malononitrile, methyl cyanoacetate, benzyl cyanide and 4-nitrobenzyl cyanide. This reaction was performed in ethanol in the presence of basic catalysts of which sodium ethoxide proved to be the best one. 2-Cyano-3-(5-heteroarylthio-2-furyl)acrylonitriles (Table I,



R = 2-Benzimidazolyl, 2-benzoxazolyl, 2-benzthiazolyl, 2-benzselenazolyl,
2-pyrimidinyl

Y = CN, COOCH₃, C₆H₅, 4-NO₂-C₆H₄

SCHEME 1

* Part CVI in the series Furan Derivatives; Part CV: This Journal 42, 3175 (1977).

TABLE I
Properties and Analytical Data of 2-Y-3-(5-R-Thio-2-furyl)acrylonitriles

No	R ^a Y	Formula (mol.w.)	M.p., °C yield, %	Calculated/Found			
				% C	% H	% N	% S
1	2-BI	C ₁₅ H ₈ N ₄ OS (292·3)	216—217 ^b	61·64	2·76	19·17	10·97
	CN		62	61·48	2·63	19·21	10·74
2	2-BO	C ₁₅ H ₇ N ₃ O ₂ S (293·3)	137—139 ^b	60·43	2·41	14·33	10·93
	CN		67	60·23	2·37	14·18	10·75
3	2-BT	C ₁₅ H ₇ N ₃ OS ₂ (309·3)	132—133 ^c	58·25	2·28	13·58	20·73
	CN		58	58·18	2·09	13·40	20·58
4	2-BS	C ₁₅ H ₇ N ₃ OSSe (351·2)	144—146 ^c	51·30	2·01	11·96	9·13
	CN		63	51·24	1·95	11·74	9·16
5	2-PY	C ₁₂ H ₆ N ₄ OS (249·2)	125—126 ^b	57·84	2·43	22·48	12·87
	CN		65	57·84	2·48	22·31	12·66
6	2-BI	C ₁₆ H ₁₁ N ₃ O ₃ S (325·3)	211—213 ^b	59·08	3·41	12·92	9·86
	COOCH ₃		57	58·86	3·36	12·86	9·78
7	2-BO	C ₁₆ H ₁₀ N ₂ O ₄ S (326·3)	112—113 ^c	58·90	3·09	8·58	9·83
	COOCH ₃		61·5	58·78	2·96	8·41	9·78
8	2-BT	C ₁₆ H ₁₀ N ₂ O ₃ S ₂ (342·3)	111—112 ^b	56·14	2·94	8·18	18·74
	COOCH ₃		56·5	56·12	2·86	8·21	18·48
9	2-BS	C ₁₆ H ₁₀ N ₂ O ₃ SSe (389·2)	127—128 ^b	49·38	2·59	7·20	8·24
	COOCH ₃		55	49·15	2·47	7·22	8·18
10	2-PY	C ₁₃ H ₉ N ₃ O ₃ S (287·2)	139—140 ^b	54·37	3·16	14·63	11·17
	COOCH ₃		62·5	54·21	3·02	14·51	10·98
11	2-BI	C ₂₀ H ₁₃ N ₃ OS (343·4)	245—247 ^b	69·95	3·82	12·24	9·34
	C ₆ H ₅		88·4	69·74	3·75	12·08	9·35
12	2-BO	C ₂₀ H ₁₂ N ₂ O ₂ S (344·3)	166—168 ^c	69·77	3·51	8·14	9·31
	C ₆ H ₅		74·5	69·68	3·47	8·02	9·21
13	2-BT	C ₂₀ H ₁₂ N ₂ OS ₂ (360·4)	228—230 ^c	66·65	3·36	7·77	17·79
	C ₆ H ₅		66·6	66·55	3·22	7·82	17·91
14	2-BS	C ₂₀ H ₁₂ N ₂ OSSe (407·3)	197—199 ^c	58·98	2·97	6·88	7·87
	C ₆ H ₅		64·7	58·74	2·88	6·78	7·75
15	2-PY	C ₁₇ H ₁₂ N ₃ OS (306·3)	158—160 ^b	66·66	3·95	13·72	10·47
	C ₆ H ₅		71	66·51	3·89	13·70	10·41
16	2-BI	C ₂₀ H ₁₂ N ₄ O ₃ S (388·4)	234—236 ^b	61·85	3·11	14·42	8·26
	4-NO ₂ C ₆ H ₄		74·5	61·77	2·98	14·32	8·09
17	2-BO	C ₂₀ H ₁₁ N ₃ O ₄ S (389·3)	210—212 ^c	61·71	2·85	10·79	8·24
	4-NO ₂ C ₆ H ₄		72·8	61·55	2·82	10·71	8·18

TABLE I
(Continued)

No	R ^a Y	Formula (mol.w.)	M.p., °C yield, %	Calculated/Found			
				% C	% H	% N	% S
18	2-BT	C ₂₀ H ₁₁ N ₃ O ₃ S ₂	194–196 ^c	59.26	2.74	10.36	15.82
	4-NO ₂ C ₆ H ₄	(405.4)	67.5	59.11	2.56	10.27	15.61
19	2-BS	C ₂₀ H ₁₁ N ₃ O ₃ SSe	179–180 ^a	53.11	2.45	9.29	7.09
	4-NO ₂ C ₆ H ₄	452.3	71.2	52.88	2.41	9.15	7.12
20	2-PY	C ₁₇ H ₁₀ N ₄ O ₃ S	206–207 ^b	58.12	2.87	15.95	9.13
	4-NO ₂ C ₆ H ₄	351.3	74.8	58.05	2.82	15.77	9.16

^a 2-BI 2-Benzimidazolyl, 2-BO 2-benzoxazolyl, 2-BT 2-benzthiazolyl, 2-BS 2-benzselenazolyl, 2-PY 2-pyrimidinyl; ^b crystallized from ethanol; ^c crystallized from acetone.

compounds 1–5) and methyl 2-cyano-3-(5-heteroarylthio-2-furyl)acrylates (Table I, compounds 6–10) were prepared also by the reaction of 2-cyano-3-(5-bromo-2-furyl)acrylonitrile or methyl acrylate with sodium salts of the corresponding thiols in ethanol in 40–50% yields (Scheme 1). Physical constants and analytical data of the condensation products are given in Table I. All the prepared compounds are solids and their solutions exhibit strong fluorescence.

Kinetic studies were performed in order to assess how the reactivity of the carbonyl group is affected by a heteroaryl group bonded through the sulphur atom to the position 5 of the furan ring. The reaction was followed spectrophotometrically, using the K-band of the formed condensation product, under conditions of a pseudomonomolecular reaction (excess of the methylene component). We found that, as expected, the rates of reactions between 5-heteroarylthio-2-furaldehydes and compounds containing active methylene group are affected both by reactivity of the formed carbanion and by the charge deficit on the carbonyl carbon of the aldehyde. Concerning the methylene component, the observed rate constants decreased in the order malononitrile, methyl cyanoacetate, 4-nitrobenzyl cyanide. From our results it follows that the condensation rates parallel the p*K* values of the methylene hydrogens as well as the steric demands of the carbanion. We tried to determine also the rate of the reaction with benzyl cyanide. Although the corresponding carbanion can be formed, the condensation was extremely sluggish under the given conditions (25°C). Of the heterocyclic substituents in the position 5 of the 2-furaldehyde, the benzimidazole moiety exhibits the greatest effect on the carbonyl reactivity. The reactivity of other studied aldehydes decreases with the decreasing electronegativity of the hetero atom built into the azole system: NH > O > S > Se.

TABLE II

UV-Spectral Data of the Derivatives 1–20 and the Rate Constants (s^{-1}) for the Corresponding Condensation Reactions

No	λ_{\max} , nm (log ϵ)	$k' \cdot 10^3 s^{-1}$	$t_{1/2}$ s		
1	215; 248 sh (4.23; 3.88)	284; 286 (3.97; 3.98)	370 (4.11)	50.50 ± 0.005	13.7
2	242 (4.03)	276; 282 (3.91; 3.90)	352 (4.18)	34.66 ± 0.005	19.9
3	224; 243 sh (4.26; 4.00)	274 (4.03)	354 (4.23)	24.00 ± 0.001	28.8
4	248 sh; 230 (4.05; 4.32)	280 (4.03)	351 (4.24)	19.00 ± 0.020	36.4
5	233 (4.03)	272 (3.66)	359 (4.31)	20.83 ± 0.0002	33.3
6	214; 249 sh (4.39; 4.00)	282; 287 (4.12; 4.14)	357 (4.30)	28.21 ± 0.0022	24.5
7	214; 242 (4.24; 4.19)	275; 282 (4.08; 4.08)	344 (4.26)	2.51 ± 0.001	276.0
8	222; 243 sh (4.38; 4.00)	273 (4.03)	346 (4.26)	1.81 ± 0.0012	382.8
9	229; 248 sh (4.46; 4.12)	281 (4.11)	345 (4.34)	1.02 ± 0.003	679.0
10	221; 243 sh (4.29; 3.89)	273 (3.92)	345 (3.92)	10.50 ± 0.004	66.0
11	219 (4.46)	247 (4.39)	307 (4.66)	—	—
12	243 (4.21)	276; 283 (4.05; 4.05)	348 (4.30)	—	—
13	224; 243 sh (4.33; 4.20)	271; 299 sh (4.16; 3.94)	343 (4.03)	—	—
14	234 (4.18)	—	351 (4.15)	—	—
15	247; 231 (4.21; 4.35)	279 (4.11)	345 (4.22)	—	—
16	214; 253 (4.39; 4.19)	282; 287 (4.28; 4.28)	373 (4.14)	0.66 ± 0.001	1 050.0
17	244 (4.20)	275; 283 (4.19; 4.18)	360 (4.12)	0.215 ± 0.005	3 228.8

TABLE II
(Continued)

No	λ_{\max} , nm (log ϵ)		k' , 10^3 s^{-1}	$t_{1/2}$ s
18	224; 244 sh (4.34; 4.13)	273; 298 sh (4.19; 4.05)	371 (4.28)	0.080 ± 0.001 —
19	230; 248 (4.37; 4.22)	276 (4.23)	362 (4.13)	0.107 ± 0.0008 6 476.2
20	234 (4.18)	270 (4.07)	369 (4.12)	0.312 ± 0.0001 2 221.1

EXPERIMENTAL

The 5-heteroarylthio-2-furaldehydes employed in the study were prepared by the reaction of alkali salts of the heterocyclic thiols with 5-bromo- or 5-iodo-2-furaldehyde in dimethylformamide¹. Malononitrile, methyl cyanoacetate, 4-nitrobenzyl cyanide and benzyl cyanide were commercial products.

Condensation Reactions

A solution of 0.01 mol of the methylene component (*i.e.* 0.66 g of malononitrile, 0.99 g of methyl cyanoacetate, 1.6 g of 4-nitrobenzyl cyanide or 1.17 g of benzyl cyanide) in ethanol (10 ml) was added to a solution of the corresponding aldehyde (0.01 mol) in ethanol (25–50 ml, depending on the solubility of the aldehyde). The mixture was stirred and about 5 drops of a 10% solution of sodium ethoxide were added. After 1 min the product began to precipitate and the mixture was set aside for 3 h at room temperature. The product was filtered and washed with cold ethanol (10 ml). Further amount of the product was precipitated by addition of water to the filtrate. The crude product was crystallized from an appropriate solvent.

Kinetic Measurements

UV spectra, as well as kinetic measurements, were taken on a Specord UV VIS recording spectrophotometer in the region 200–800 nm. The samples were measured in 1 cm thermostated cells in methanol; concentration $2-5 \cdot 10^{-5} \text{ M}$. The rate constants were determined at $25 \pm 0.2^\circ \text{C}$ in a mixture of the methylene component (2 ml; concentration in the reaction mixture $2 \cdot 10^{-3} \text{ M}$), 0.2–0.4 ml of a methanolic solution of the aldehyde (concentration in the reaction mixture $2-4 \cdot 10^{-5} \text{ M}$), 5 ml of a 0.05M solution of pyridine in methanol and 2.6 ml (or 2.8 ml) of methanol. The same mixture (without the aldehyde) was used as a blank. The kinetic measurements were taken at the wavelength of the K-band of the condensation product and the rate constants were calculated from the linear plot $\log \Delta E$ against time, using the equation for a first-order

reaction. The UV spectral data of the condensation products, the rate constants, k' (s^{-1}), and the half-lives, $t_{1/2}$ (s), for the condensation of 5-heteroarylthio-2-furaldehydes with compounds containing an active methylene group are given in Table II.

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Translated by M. Tichý.