# STUDY OF THE CONDENSATION OF 5-ARYLTHIO-2-FURALDEHYDES WITH COMPOUNDS WITH ACTIVE METHYLENE GROUP

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On reaction of 5-(4-X-phenylthio)-2-furaldehydes with malonic acid dinitrile, methyl cyanoaceta-te, benzyl cyanide, and 4-nitrobenzyl cyanide in methanol and in the presence of basic catalysts the corresponding α-substituted 5-(4-X-phenylthio)-2-furylacrylonitriles were prepared. In addition to the synthesis their UV spectra as well as kinetic measurements of the condensation reaction course are also described. The effect of substituents bound to the arylthio group on the condensation rate is also discussed.

In connection with the study of the synthesis, physico-chemical and biological properties of sulfur derivatives of furan we described in our preceding paper[1] the preparation of 5-(4-X-phenylthio)-2-furaldehydes where X represents the electron acceptor or electron donor substituents, respectively. In this paper we investigate the condensation of these aldehydes with compounds containing an active methylene group of the type Y—CH$_2$—CN, where Y = CN, COOCH$_3$, C$_6$H$_5$ and 4-NO$_2$—C$_6$H$_4$, not yet described in literature. The course of this condensation reaction was followed kinetically with the aim of judging the influence of the reaction rate both by the methylene component and from the point of view of the reactivity of the corresponding aldehydes.

The synthetized α-Y-substituted 5-(3-X-phenylthio)-2-furylacrylonitriles were obtained from corresponding 5-(4-X-phenylthio)-2-furaldehydes and malonic acid dinitrile, or methyl cyanoacetate, benzyl cyanide and 4-nitrobenzyl cyanide under the conditions of Knoevenagel condensation — on reaction in ethanol under catalysis with basic catalysts (method A). Piperidine and sodium ethoxide were used as catalysts with advantage. In all instances corresponding condensation products were obtained in high yields (70−90%). All compounds are yellow and strongly fluoresce in solutions. α-Cyano-5-(4-X-phenylthio)-2-furylacrylonitriles and methyl α-cyano-5-(4-X-phenylthio)-2-furylacrylates were also prepared on reaction of α-cyano-(5-bromo-2-furyl)acrylonitrile or methyl α-cyano-(5-bromo-2-furyl)acrylate with the sodium salt of the corresponding thiol in ethanol in 40−50% yields (Method B), see Table I.

In the UV spectra of the condensation products of 5-(4-X-phenylthio)-2-furalde-hydes with malonic acid dinitrile, methyl cyanoacetate) 4-nitrobenzyl cyanide and benzyl cyanide a strongly bathochromically shifted K-band appeared in consequence of the extention of the conjugated system, in contrast to the original aldehydes. The position of this band is affected by substituents in the position 4 of the benzene nucleus. From comparison with analogous condensation products of 5-(4-X-phenyl)--2-furaldehydes[2] it follows that the K-band corresponding to the delocalisation of the electrons over the whole system of the molecule is considerably shifted batho-chromically in molecules without a sulfide bridge, and it appears in the visible part of the spectrum, see Table I.

Observation of the course of the condensation reactions in time was carried out spectrophotometrically making use of the fact that in the K-band region of the con-densation product formed ($\sim$400 nm) the absorption band was not present either in the case of the aldehyde or of the methylene component. Kinetic measurements were carried out in methanolic solution of piperidine under the conditions of pseudo-monomolecular reaction, when an excess of the methylene component was taken. From comparison of the rate constants of the reaction with single compounds con-taining active methylene group (Table II) it is evident that the rate of this condensa-tion reaction affects both the reactivity of the carbanion formed and also the deficit of the charge on the carbonyl group carbon of the substituted 2-furaldehyde. From the point of view of the methylene component the highest rate constants were obtained in the reaction of aldehydes with malonic acid dinitrile, lower values were observed with methyl cyanoacetate, and the lowest with 4-nitrobenzyl cyanide. From the comparison of the results obtained it is evident that the rate of condensation reac-
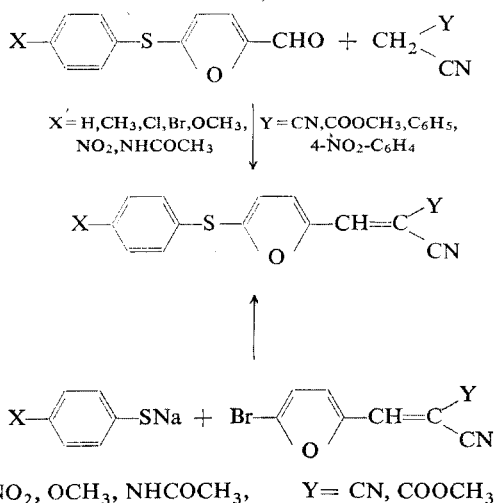


$$X = H, CH_3, Cl, Br, OCH_3, \quad Y = CN, COOCH_3, C_6H_5,$$
$$NO_2, NHCOCH_3 \qquad 4\text{-}NO_2\text{-}C_6H_4$$

$$X = H, CH_3, Cl, Br, NO_2, OCH_3, NHCOCH_3, \qquad Y = CN, COOCH_3$$

TABLE I

Synthetized $\alpha$-Y-Substituted 5-(4-X-Phenylthio)-2-furylacrylonitriles and the Values of Their UV and IR Spectral Data

| No | X<br>Y | Composition<br>(m.w.) | M.p., °C<br>(Yield, %) | Calculated/Found | | | | $\lambda_{max}$, nm log $\epsilon$ | | | $\nu(C\equiv N)$<br>$(cm^{-1})$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | % C | % H | % N | % S | | | | |
| 1 | H<br>CN | $C_{14}H_8N_2OS$<br>(252·3) | 85[a]<br>(81·5) | 66·65<br>66·48 | 3·20<br>3·05 | 11·10<br>11·15 | 12·71<br>12·62 | 211<br>4·13 | 242 r<br>3·96 | 394<br>4·33 | 2 236 |
| 2 | CH₃<br>CN | $C_{15}H_{10}N_2OS$<br>(266·3) | 87—88[a]<br>(76·5) | 67·65<br>67·55 | 3·78<br>3·64 | 10·52<br>10·42 | 12·04<br>11·87 | 212<br>4·15 | 224; 243 r<br>4·16; 3·94 | 395<br>4·21 | 2 234 |
| 3 | CH₃O<br>CN | $C_{15}H_{10}N_2O_2S$<br>(282·3) | 73—74[a]<br>(77·5) | 63·82<br>63·56 | 3·57<br>3·49 | 9·92<br>9·78 | 11·36<br>11·24 | 209<br>4·13 | 233<br>4·28 | 407<br>4·34 | 2 234 |
| 4 | CH₃CONH<br>CN | $C_{16}H_{11}N_3O_2S$<br>(309·3) | 167—169[b]<br>(84·7) | 62·13<br>61·88 | 3·58<br>3·42 | 13·58<br>13·35 | 10·37<br>10·13 | 210<br>4·33 | 253<br>4·31 | 401<br>4·31 | 2 234 |
| 5 | Cl<br>CN | $C_{14}H_7ClN_2OS$<br>(286·7) | 96—98[a]<br>(83·6) | 58·65<br>58·52 | 2·46<br>2·37 | 9·77<br>9·72 | 11·18<br>11·12 | 210<br>4·0 | 227; 243 r<br>4·15; 3·94 | 385<br>4·25 | 2 234 |
| 6 | Br<br>CN | $C_{14}H_7BrN_2OS$<br>(331·2) | 130—132[a]<br>(82·8) | 50·77<br>50·48 | 2·13<br>2·04 | 8·46<br>8·41 | 9·68<br>9·58 | 205<br>4·54 | 229; 244 r<br>4·48; 4·34 | 395<br>4·43 | 2 234 |
| 7 | NO₂<br>CN | $C_{14}H_7N_3O_3S$<br>(297·3) | 203—205[a]<br>(89·2) | 56·56<br>56·31 | 2·37<br>2·17 | 14·13<br>14·02 | 10·78<br>10·72 | 204<br>4·35 | —<br>— | 370<br>4·26 | 2 235 |
| 8 | H<br>COOCH₃ | $C_{15}H_{11}NO_3S$<br>(285·3) | 95—97[a]<br>(72·7) | 63·15<br>62·94 | 3·89<br>3·72 | 4·91<br>4·88 | 11·24<br>11·05 | 210<br>4·22 | 241 r<br>4·0 | 371<br>4·33 | 2 230 |
| 9 | CH₃<br>COOCH₃ | $C_{16}H_{13}NO_3S$<br>(299·3) | 71[a]<br>(73·5) | 64·21<br>64·04 | 4·38<br>4·26 | 4·68<br>4·53 | 10·71<br>10·05 | 205<br>4·40 | 242; 222<br>4·12; 4·33 | 394<br>4·41 | 2 228 |
| 10 | CH₃O<br>COOCH₃ | $C_{16}H_{13}NO_4S$<br>(315·3) | 79—80[a]<br>(71·8) | 60·95<br>60·72 | 4·16<br>3·98 | 4·44<br>4·28 | 10·17<br>10·55 | 204<br>4·40 | 233<br>4·33 | 398<br>4·36 | 2 230 |

TABLE I
(Continued)

| No | X / Y | Composition (m.w.) | M.p., °C (Yield, %) | % C | % H | % N | % S | λmax, nm log ε | νC≡N (cm⁻¹) |
|----|-------|--------------------|--------------------|-----|-----|-----|-----|----------------|-------------|
| 11 | $CH_3CONH$ / $COOCH_3$ | $C_{17}H_{14}N_2O_4S$ (342·4) | 139—141[b] (81·5) | 59·63 / 59·41 | 4·12 / 4·06 | 8·18 / 8·07 | 9·36 / 9·26 | 207 4·59; 254 4·45; 393 4·42 | 2 230 |
| 12 | $Cl$ / $COOCH_3$ | $C_{15}H_{10}ClNO_3S$ (319·8) | 113—114[a] (83·6) | 56·34 / 56·18 | 3·15 / 3·11 | 4·38 / 4·29 | 10·03 / 9·92 | 205 4·32; 227; 247 4·23; 4·04; 372 4·29 | 2 230 |
| 13 | $Br$ / $COOCH_3$ | $C_{15}H_{10}BrNO_3S$ (364·2) | 126—128[a] (81·4) | 49·47 / 49·31 | 2·77 / 2·58 | 3·85 / 3·74 | 8·80 / 8·91 | 204 4·36; 231; 253 4·24; 4·04; 374 4·28 | 2 230 |
| 14 | $NO_2$ / $COOCH_3$ | $C_{15}H_{10}N_2O_5S$ (330·3) | 213—214[a] (94·5) | 54·54 / 54·52 | 3·05 / 2·94 | 8·48 / 8·38 | 9·71 / 9·62 | 208 4·21; 362 r; 357 4·13; 4·33 | 2 230 |
| 15 | $H$ / $C_6H_5$ | $C_{19}H_{13}NOS$ (303·4) | 95—96[a] (87·1) | 75·22 / 75·05 | 4·32 / 4·18 | 4·62 / 4·55 | 10·57 / 10·38 | 210 4·25; 241 4·25; 362 4·49 | 2 220 |
| 16 | $CH_3$ / $C_6H_5$ | $C_{20}H_{15}NOS$ (317·4) | 71—72[a] (86·2) | 75·68 / 75·42 | 4·76 / 4·56 | 4·41 / 4·28 | 10·10 / 10·16 | 208 4·36; 243 4·26; 361 4·44 | 2 220 |
| 17 | $CH_3O$ / $C_6H_5$ | $C_{20}H_{15}NO_2S$ (333·4) | 81—82[a] (78·5) | 72·05 / 71·83 | 4·54 / 4·36 | 4·20 / 4·08 | 9·62 / 9·58 | 210 4·23; 236 4·29; 368 4·36 | 2 220 |
| 18 | $CH_3CONH$ / $C_6H_5$ | $C_{21}H_{16}N_2O_2'S$ (360·4) | 85—87[a] (82·4) | 69·98 / 69·75 | 4·47 / 4·28 | 7·77 / 7·58 | 8·90 / 8·76 | 210 4·47; 247; 260 4·43; 4·41; 362 4·51 | 2 220 |
| 19 | $Cl$ / $C_6H_5$ | $C_{19}H_{12}ClNOS$ (337·8) | 91—92[a] (77·3) | 67·56 / 67·48 | 3·58 / 3·54 | 4·15 / 4·12 | 9·49 / 9·48 | 210 4·30; 232; 246 4·29; 4·30; 347 4·34 | 2 220 |

| No. | R | Formula (M.W.) | M.p. (%) | % C | % H | % N | % S | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Br C$_6$H$_5$ | C$_{19}$H$_{12}$BrNOS (382·3) | 80—81$^a$ (75·5) | 59·69 / 59·52 | 3·16 / 3·14 | 3·66 / 3·52 | 8·39 / 8·21 | 210 / 3·96 | 238 / 3·92 | 359 / 4·11 | 2 220 |
| 21 | NO$_2$ C$_6$H$_5$ | C$_{19}$H$_{12}$N$_2$O$_3$S (348·4) | 110—112$^a$ (89·6) | 65·50 / 65·33 | 3·47 / 3·28 | 8·04 / 8·10 | 9·20 / 9·16 | 207 / 4·28 | 236 / 4·10 | 357 / 4·46 | 2 222 |
| 22 | H p-NO$_2$–C$_6$H$_4$ | C$_{19}$H$_{12}$N$_2$O$_3$S (348·4) | 113—114$^a$ (91·7) | 65·50 / 65·29 | 3·47 / 3·36 | 8·04 / 7·94 | 9·20 / 9·26 | 211 / 4·34 | 242 r / 4·20 | 390 / 4·52 | 2 224 |
| 23 | CH$_3$ p-NO$_2$–C$_6$H$_4$ | C$_{20}$H$_{14}$N$_2$O$_3$S (362·4) | 132—134$^a$ (88·7) | 66·28 / 66·06 | 3·89 / 3·78 | 7·73 / 7·71 | 8·85 / 8·71 | 211; 224 / 4·35; 4·33 | 242 r / 4·21 | 393 / 4·46 | 2 222 |
| 24 | CH$_3$O p-NO$_2$–C$_6$H$_4$ | C$_{20}$H$_{14}$N$_2$O$_4$S (378·4) | 123—125$^a$ (85·5) | 63·48 / 63·37 | 3·69 / 3·54 | 7·40 / 7·36 | 8·47 / 8·53 | 212 / 4·29 | 234 / 4·35 | 399 / 4·46 | 2 221 |
| 25 | CH$_3$CONH p-NO$_2$–C$_6$H$_4$ | C$_{21}$H$_{15}$N$_3$O$_4$S (405·4) | 96—98$^a$ (84·3) | 62·22 / 62·05 | 3·73 / 3·61 | 10·36 / 10·28 | 7·91 / 7·78 | 210 / 4·44 | 255 / 4·39 | 393 / 4·48 | 2 222 |
| 26 | Cl p-NO$_2$–C$_6$H$_4$ | C$_{19}$H$_{11}$ClN$_2$O$_3$S (382·8) | 125—126$^a$ (85·7) | 59·61 / 59·48 | 2·90 / 2·78 | 7·32 / 7·18 | 8·38 / 8·16 | 211 / 4·34 | 250 r; 230 / 4·19; 4·32 | 388 / 4·49 | 2 223 |
| 27 | Br p-NO$_2$–C$_6$H$_4$ | C$_{19}$H$_{11}$BrN$_2$O$_3$S (427·3) | 123—125$^a$ (84·5) | 53·41 / 53·36 | 2·59 / 2·41 | 6·55 / 6·44 | 7·50 / 7·42 | 212 / 4·31 | 233; 253 r / 4·29; 4·15 | 388 / 4·45 | 2 223 |
| 28 | NO$_2$ p-NO$_2$–C$_6$H$_4$ | C$_{19}$H$_{11}$N$_3$O$_5$S (393·4) | 145—147$^c$ (92·7) | 58·01 / 57·88 | 2·82 / 2·78 | 10·68 / 10·56 | 8·15 / 8·17 | 207 / 4·29 | 305 r / 4·11 | 378 / 4·34 | 2 223 |

$^a$ Crystallized from ethanol; $^b$ from benzene; $^c$ from acetic acid.

tion is in agreement with the $pK_a$ values of the hydrogens of the methylene component $(pK_a$ of malonic acid dinitrile is 11·16, of methyl cyanoacetate 11·50, and of 4-nitrobenzyl cyanide 13·4) and simultaneously with the sterical requirements of the carbanion formed. The corresponding condensation reaction with benzyl cyanide under the conditions used was extramely slow. When the temperature was increased to 55°C the rate was measurable, but only in the case of aldehydes with electron accepting substituents, for example in the case of 5-(4-nitrophenylthio)-2-furaldehyde the rate constant is $0·26 . 10^{-4} s^{-1}$, which is substantially lower in comparison with the reaction of the last reactive 4-nitrobenzyl cyanide with the same aldehyde.

When the effect was observed of the substituent in the position 4 of the phenylthio residue on the electron density of the carbonyl carbon of 2-furaldehyde via the sulfur atom, and thus on the condensation reaction rate, it was found that it is only roughly true that the electron donating substituents decrease, and the electron accepting substituents increase the condensation rate. In agreement with these conclusions the correlation of the logarithm of rate constants with Hammett's $\sigma_p$ constants

TABLE II

Rate Constants $k'$ $(s^{-1})$ and Half-Times $t_{1/2}$ (s) of the Condensation Reaction of 5-(4-X-Phenylthio)-2-furaldehydes with Compounds of Type $Y-CH_2-CN$

| No | X | $Y = CN$ $k' . 10^4$ | $t_{1/2}$ | $Y = COOCH_3$ $k' . 10^4$ | $t_{1/2}$ | $Y = 4\text{-}NO_2-C_6H_4$ $k' . 10^4$ | $t_{1/2}$ |
|---|---|---|---|---|---|---|---|
| 1 | $NO_2$ | $520·8 \pm 0·020$ | 13·3 | $161·02 \pm 0·002$ | 43·0 | $8·90 \pm 0·005$ | 770 |
| 2 | Cl | $150·17 \pm 0·005$ | 46·1 | $62·90 \pm 0·005$ | 110·1 | $4·60 \pm 0·001$ | 1 506 |
| 3 | Br | $198·0 \pm 0·001$ | 35·0 | $49·50 \pm 0·004$ | 140·2 | $5·36 \pm 0·002$ | 1 292 |
| 4 | $CH_3CONH$ | $85·5 \pm 0·003$ | 81·0 | $46·98 \pm 0·002$ | 147·5 | $4·31 \pm 0·005$ | 1 607 |
| 5 | H | $93·67 \pm 0·004$ | 74·0 | $41·28 \pm 0·0003$ | 167·8 | $4·83 \pm 0·005$ | 1 434 |
| 6 | $CH_3$ | $86·00 \pm 0·0025$ | 80·6 | $31·33 \pm 0·001$ | 221·1 | $4·42 \pm 0·002$ | 1 568 |
| 7 | $CH_3O$ | $73·00 \pm 0·001$ | 94·9 | $21·50 \pm 0·002$ | 322·3 | $3·92 \pm 0·001$ | 1 768 |

TABLE III

Kinetic Values of the Reaction of 5-Phenylseleno-2-furaldehyde with $Y-CH_2-CN$

| Y | CN | $COOCH_3$ | $4\text{-}NO_2-C_6H_4$ |
|---|---|---|---|
| $k' . 10^4$ $(s^{-1})$ | $39·33 \pm 0·05$ | $35·17 \pm 0·001$ | $4·47 \pm 0·001$ |
| $t_{1/2}$ (s) | 176·2 | 197·0 | 1 550·3 |

of substituents[3] is also good. The correlation values of the reaction of 5-(4-X-phenyl-thio)-2-furaldehydes with malonic acid dinitrile is $r = 0.98$ and $\varrho = 0.85$, with methyl cyanoacetate $r = 0.98$ and $\varrho = 0.77$, and with 4-nitrobenzyl cyanide $r = 0.95$ and $\varrho = 0.33$. At a chosen level of significance $p = 0.01$, when in all three instances $r > r_{0.01}$, we consider the existence of the investigated dependence as conclusive. In all three correlations the number of derivatives was 7. The low value of $\varrho$ in the case of the reaction with 4-nitrobenzyl cyanide may be explained on the basis of the larger volume of the carbanion formed, as well as on the basis of the possibility of a larger delocalization of the negative charge in the system formed in contrast to the further two mentioned carbanions.

For the sake of comparison the rate of the condensation reaction of 5-phenylseleno--2-furaldehyde with the above mentioned methylene components was also followed. From the results of kinetic measurements (Table III) it follows that in all instances the rate constants of the selenium derivative are lower; this is probably due to the lower reactivity of the carbonyl group of 5-phenylseleno-2-furaldehyde, caused by a better interaction of free electron pairs of selenium with the $\pi$-electron system of the furan nucleus.

## EXPERIMENTAL

The 5-(4-X-phenylthio)-2-furaldehydes used were prepared by reaction of the corresponding sodium salt of 4-X-substituted thiophenol with 5-bromo or 5-iodo-2-furaldehyde in ethanol[1]. As a model substance for kinetic measurements 5-phenylseleno-2-furaldehyde was prepared from selenophenol and 5-bromo-2-furaldehyde in acetone in the presence of anhydrous potassium carbonate[1]. The necessary selenophenol was prepared from phenylmagnesium bromide and metallic selenium[4].

The infrared spectra were measured on a two-beam UR 20 spectrophotometer (Zeiss) in sodium chloride cells of 1.04 mm thickness and at 0.025M concentration in chloroform. The calibration of the apparatus was carried out using a polystyrene foil. The accuracy of the reading of frequencies was $\pm 1$ cm$^{-1}$.

### α-Y-Substituted 5-(4-X-Phenylthio)-2-furylacrylonitriles

*A*: A 0.01M solution of malonic acid dinitrile, or methyl cyanoacetate, benzyl cyanide or 4-nitrobenzyl cyanide in 10 ml of ethanol was added to a 0.01M solution of the corresponding 5-(4-X-phenylthio)-2-furaldehyde in 15—20 ml of ethanol and a drop of piperidine or sodium ethoxide was added under stirring and the mixture then stirred at room temperature for 2—3 hours. The precipitated material was filtered off, washed with cold ethanol and crystallized from a suitable solvent.

*B*: 0.01 mol of sodium 4-X-substituted thiophenolate was added under stirring to 0.01 mol of α-cyano-5-bromo, or 5-iodo-2-furylacrylonitrile or methyl acrylate dissolved in the necessary amount of ethanol and the mixture was stirred at room temperature for 3—4 hours. After dilution with cold water the precipitate was crystallized from a suitable solvent. The synthetized derivatives and their physico-chemical data are given in Table I.

Kinetic Measurements

The measurements of the UR spectra of the prepared substances, as well as kinetic measurements were carried out on a recording spectrophotometer Specord UV VIS, Zeiss, in the $200-800$ nm region. During the measurements of the UV spectra the concentration of substances in methanol was $2-5 \cdot 10^{-5}$M. Kinetic measurements were carried out at $25 \pm 0.2°$C or $55 \pm 0.2°$C in the case of the reaction with benzyl cyanide in 1 cm thermostated cells at the wavelength of the absorption maximum of the condensation product. The reaction kinetics was followed in the following mixture: 2 ml of the condensing agent (malonic acid dinitrile or methyl cyanoacetate, benzyl cyanide or 4-nitrobenzyl cyanide, resulting concentration in the mixture was $2 \cdot 10^{-3}$M), 5 ml of 0·05M piperidine in methanol (resulting concentration in the mixture $2.5 \cdot 10^{-2}$M), and $0.2-03·$ ml of a methanolic solution of aldehyde (resulting concentration $2-3 \cdot 10^{-5}$M), and 2·6 or 2·7 ml of methanol. The measurements were carried out in comparison with the same mixture without the aldehyde. The rate constants were calculated on the basis of a first order equation. The values of the rate constants and the half-times are given in Table II.

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