PREPARATION AND PROPERTIES OF CHALCONES OF THE FURAN SERIES

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Preparation and reactions of 1-(5-X-2-furyl)-2-methylsulfonyl-2-furoyl or -2-thienylethylenes with nucleophilic reagents are described. Stereochemistry of selected compounds was studied by NMR spectroscopy.

The biological activity of derivatives of 5-nitro-2-furaldehyde, stabilized by condensation with various substrates under formation of 5-nitrofurylethylenes and azomethines, is well known[1 - 5]. Also sulfones are biologically active, representing a large group of successfully employed chemotherapeutics[6].

The β-keto sulfones of the furylethylene series prepared by us contain in their molecule the biologically active sulfonyl group and selected compounds combine two active centers: the sulfonyl group and the nitrofuryl moiety.

In the present study we have found that introduction of a CO group into the molecule of the hitherto investigated furan sulfones lowered significantly their reactivity in condensation reactions. In the preparation of the α,β-unsaturated sulfones – chalcones – we employed successfully the Lehnert modification[7 - 9] of the Knoevenagel condensation. The prepared chalcones were further studied in reactions with nucleophilic reagents.

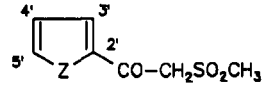
Similarly as in our previous study[10], we have found that in reactions with nucleophilic reagents the synthesized 1-(5-X-2-furyl)-2-methylsulfonyl-2-furoylethylenes exhibit low reactivity. Oxygen and sulfur nucleophiles attacked the substrates in the position 5 of furan; giving the nucleophilic substitution products in 2 – 4 days (as monitored by thin-layer chromatography).

Another behaviour of chalcones was observed in reaction with secondary amines which afforded the corresponding aminals in good yields (about 60%). The obtained 2-(di-Y)methyl-5-X-furans, where X = Br, NO_2, PhS, $PhSO_2$ and Y = diethylamine, pyrrolidine, piperidine, morpholine or N-phenylpiperazine, have already been described in our previous papers[10,18]. In the reaction with diethylamine we isolated, beside the aminal, also 23% of the nucleophilic substitution product.

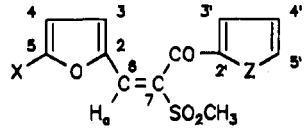
Because the studied chalcones have four possible positions for a nucleophilic attack, we subjected the reaction mixtures to a thorough analysis. In addition to the aminals and/or products of the nucleophilic reaction, we isolated and proved the unreacted 1-(5-X-2-furyl)-2-methylsulfonyl-2-furoylethylenes, the original 5-X-2-furancarbaldehydes and 2-(2-furyl)-2-oxoethyl methyl sulfone.

The structure of the newly synthesized compounds was confirmed by elemental and spectral analysis. The characteristic spectral data are given in Tables I – IV.

For selected derivatives the spectral data were supplemented by ^{13}C NMR analyses (Table V) and mass spectra. The most intensive ions are listed in Table VI.



I, Z = O
II, Z = S



	X
III	Br
IV	NO_2
V	C_6H_5S
VI	$C_6H_5SO_2$
VII	Br
VIII	$C_6H_5SO_2$
IX	C_6H_5O
X	$2\text{-}NO_2C_6H_4O$
XI	$3\text{-}NO_2C_6H_4O$
XII	$4\text{-}NO_2C_6H_4O$
XIII	CH_3S
XIV	CH_3SO_2

	X
XV	$4\text{-}CH_3CONHC_6H_4S$
XVI	1-methyl-2-imidazolylthio
XVII	2-furylmethylthio
XVIII	$(C_2H_5)_2N$

In formulae
III–VI, *IX–XVIII* : Z = O
VII, *VIII* : Z = S

TABLE I
1-(5-X-2-furyl)-2-methylsulfonyl-2-furoyl and 2-thienocarbonylethylenes

Compound	Formula (M. w.)	M. p., °C Yield, %	Calculated/Found		
			% C	% H	% S
III	$C_{12}H_9BrO_5S$	125 – 126	41.76	2.63	9.29
	(345.2)	50	42.06	2.95	9.31
IV	$C_{12}H_9NO_7S$	164 – 165	46.30	2.91	10.30
	(311.3)	42	46.61	3.13	10.70
V	$C_{18}H_{14}O_5S_2$	124 – 125	57.74	3.77	17.13
	(374.4)	47	57.85	3.81	17.56
VI	$C_{18}H_{14}O_7S_2$	183 – 184	53.19	3.47	15.78
	(406.4)	37	53.26	3.49	15.84
VII[a]	$C_{12}H_9BrO_4S_2$	114 – 115	39.90	2.51	17.75
	(361.2)	59	39.63	2.82	17.83
VIII[a]	$C_{18}H_{14}O_6S_3$	185 – 186	51.17	3.34	22.77
	(422.5)	42	51.57	3.46	22.70
IX	$C_{18}H_{14}O_6S$	100 – 101	60.33	3.94	8.95
	(358.4)	36	60.61	3.89	8.97
X	$C_{18}H_{13}NO_8S$	129 – 130	53.60	3.25	7.95
	(403.4)	35	53.83	3.73	7.96
XI	$C_{18}H_{13}NO_8S$	134 – 135	53.60	3.25	7.95
	(403.4)	36	53.99	3.48	7.89
XII	$C_{18}H_{13}NO_8S$	141 – 142	53.60	3.25	7.95
	(403.4)	41	53.68	3.64	7.94
XIII	$C_{13}H_{12}O_5S_2$	118 – 119	49.99	3.87	20.53
	(312.4)	71	50.25	3.97	20.74
XIV	$C_{13}H_{12}O_7S_2$	116 – 117	45.34	3.51	18.62
	(344.4)	68	45.48	3.68	18.42
XV	$C_{20}H_{17}NO_6S_2$	159 – 160	55.67	3.97	14.86
	(431.5)	34	55.93	4.11	15.09
XVI	$C_{16}H_{14}N_2O_5S_2$	183 – 184	50.78	3.73	16.95
	(378.4)	39	50.91	3.95	17.24
XVII	$C_{17}H_{14}O_6S_2$	oil	53.96	3.73	16.95
	(378.4)	69	53.83	3.79	17.20
XVIII	$C_{16}H_{19}NO_5S$	129 – 130	56.96	5.68	9.50
	(337.4)	24	56.73	5.72	9.83

[a] The 2-furoyl group is replaced by 2-thienyl group.

In addition to the basic carbon NMR spectrum $^{13}C-\{^1H\}$, the spectra of compounds *III* and *VII* were also taken using the gated decoupling with NOE, in which all interactions $J(C,H)$ are preserved. The assignment of the carbon signals was confirmed on the basis of the direct coupling constants $^1J(C,H)$ and the characteristic splitting due to long-range interactions. The values of coupling constants were compared with the literature data[11 - 13].

Quaternary carbon atoms were identified as signals with lower intensity and their assignment was done by comparison with the chemical shifts in analogous compounds found in the literature[11 - 13]. For an unequivocal identification of quaternary carbon atoms we made use of selective INEPT experiment[14].

From undecoupled spectra we obtained the value of vicinal coupling constant $^3J(CO,H_a)$ which served for the determination of the double bond geometry. The values of these constants for *E* and *Z* isomers of ethylenic derivatives with various substituents on the double bond and for the 2-furyl- and 2-thienylethylene compounds have been studied in several papers[13 - 17]. For a *trans*-arrangement of the interacting nuclei this

TABLE II
Infrared spectral data of the synthesized compounds (ν, cm^{-1})

Compound	ν(C=O)	$\nu_{as}(NO_2)$	$\nu_s(NO_2)$	$\nu_{as}(SO_2)$	$\nu_s(SO_2)$
III	1 645	–	–	1 317	1 141
IV	1 655	1 529	1 360	1 309	1 147
V	1 638	–	–	1 310	1 135
VI	1 652	–	–	1 321	1 148
VII	1 637	–	–	1 297	1 139
VIII	1 638	–	–	1 322	1 142
IX	1 629	–	–	1 315	1 138
X	1 650	1 519	1 353	1 323	1 143
XI	1 650	1 534	1 352	1 318	1 139
XII	1 675	1 521	1 358	1 342	1 139
XIII	1 643	–	–	1 314	1 136
XIV	1 647	–	–	1 318	1 139
XV[a]	1 674	–	–	1 313	1 133
XVI	1 634	–	–	1 316	1 151
XVII	1 613	–	–	1 299	1 154
XVIII	1 628	–	–	1 315	1 140

[a] 3 340 cm^{-1} (NH) from CH_3CONH.

constant is greater than for the *cis*-arrangement: ^3J(C,H)*trans* > ^3J(C,H)*cis*; this is an analogous criterion for *E*- and *Z*- isomers as in the ^{1}H NMR spectra.

All the studied compounds were isolated as a single geometric isomer. The found value of the coupling constant $^3J(CO,H_a) = 8.7$ Hz confirms that the carbonyl group and the olefinic proton H_a are in a *trans*-arrangement and thus all the compounds are the *E*-isomers. For a *cis*-relation between carbonyl and the olefinic proton in analogous derivatives the value of $^3J(CO,H_a)$ is given[14-17] as 6 Hz.

In biologic screening, the synthesized compounds exhibited interesting properties that will be the subject of a separate communication.

EXPERIMENTAL

Infrared spectra were recorded on a Specord M 80 (Carl Zeiss, Jena) instrument using the KBr technique, UV spectra were measured on a Specord M 40 (Carl Zeiss, Jena) spectrometer in methanol at concentration $1 . 10^{-4} - 1 . 10^{-5}$ mol dm^{-3}. ^{1}H NMR spectra were taken on a Tesla BS 587A spectrometer (80 MHz)

TABLE III
Ultraviolet absorption spectra of the synthesized compounds

Compound	λ_{max}	log ε	λ_{max}	log ε	λ_{max}	log ε
III	234	2.74	284	3.29	331	3.15
IV	232	3.14	287	3.29	333	3.11
V	239	3.08	284	3.31	317	3.11
VI	231	3.18	282	3.39	319	3.24
VII	207	3.42	294	3.74	310	3.71
VIII	232	2.95	274	3.18	295	3.22
IX	221	3.11	281	3.28	300	3.40
X	227	2.90	284	3.09	310	2.88
XI	230	3.12	283	3.34	318	3.08
XII	225	3.17	284	3.32	307	3.36
XIII	233	2.78	286	3.26	300	3.19
XIV	233	2.81	284	3.28	314	3.16
XV	229	3.18	265	3.41	294	3.32
XVI	227	3.04	262	3.87	317	3.11
XVII	222	3.36	279	3.93	304	2.88
XVIII	221	3.05	285	3.16	292	3.12

and on FT spectrometers Bruker AM-300 and Varian VXR-300 in $(CD_3)_2CO$ using tetramethylsilane as internal standard. The ^{13}C NMR spectra were taken with the mentioned Bruker instrument at 75.43 MHz in $(CH_3)_2CO$. Mass spectra were measured on an MS 902-S (AEI Manchester) model; direct inlet, ionizing electron energy 70 eV, electron current 100 μA, ion source temperature 120 – 150 °C.

2-(*Z*)-Oxoethyl Methyl Sulfones *I* and *II*

A solution of 2-bromoacetylfuran or 2-bromoacetylthiophene (0.1 mol) in methanol (50 ml) was added to a stirred suspension of sodium methylsulfinate (0.11 – 0.15 mol) in dry methanol (80 ml) and the reaction mixture was refluxed for 2.5 h. After concentration, the crystalline crude product was purified by crystallization from ethanol.

2-(2-Furyl)-2-oxoethyl methyl sulfone (I): yield 48%, m.p. 122 – 123 °C. For $C_7H_8O_4S$ (188.2) calculated: 44.67% C, 4.28% H, 17.04% S; found: 44.59% C, 4.39% H, 17.51% S. IR spectrum, cm^{-1}: 1 660 (C=O), 1 320 (asym. SO_2), 1 165 (sym. SO_2). UV spectrum, nm (log ε): 227 (2.45), 281 (3.18). ^1H NMR spectrum: 3.16 s,

TABLE IV
^1H NMR spectra (δ, ppm)

Compound	CH_3	H_a	H_3	H_4	H_3'	H_4'	H_5'
III	3.24 s	7.58 s	7.11 d	6.66 d	7.34 dd	6.61 dd	7.90 d
IV	3.27 s	7.74 s	7.32 d	7.53 d	7.42 dd	6.69 dd	7.91 d
V[a]	3.23 s	7.62 s	7.19 d	6.86 d	7.29 d	6.60 dd	7.80 s
VI[b]	3.21 s	7.65 s	7.21 d	7.36 d	7.36 d	6.64 dd	7.91 s
VII	3.24 s	7.59 s	7.09 d	6.62 d	7.70 dd	7.19 dd	8.04 dd
VIII[c]	3.19 s	7.61 s	7.06 d	6.59 d	7.64 dd	7.16 dd	8.02 dd
IX[d]	3.00 s	7.08 s	6.91 s	6.48 d	6.95 d	6.77 dd	7.28 d
X[e]	3.17 s	7.52 s	7.17 d	5.91 d	7.19 d	6.49 dd	7.77 d
XI[f]	3.18 s	7.52 s	7.17 d	6.00 d	7.17 d	6.52 dd	7.78 d
XII[g]	3.29 s	7.65 s	6.99 d	6.08 d	7.14 d	6.65 dd	7.80 d
XIII[h]	3.24 s	7.58 s	7.33 d	6.67 d	7.12 d	6.70 dd	7.93 d
XIV[i]	3.19 s	7.54 s	6.92 d	6.30 d	7.29 d	6.64 dd	7.86 d
XV[j]	3.06 s	7.64 s	6.95 d	6.75 d	7.06 d	6.60 dd	7.75 d
XVI[k]	3.03 s	7.27 s	7.01 d	6.73 d	6.86 d	6.78 dd	7.41 d
XVII[l]	3.38 s	7.48 s	7.36 d	6.68 d	7.41 d	6.73 dd	7.97 d
XVIII[m]	3.33 s	7.28 s	7.13 d	5.37 d	7.20 d	6.66 dd	7.83 d

[a] PhS (7.40 – 7.15 m); [b] $PhSO_2$ (7.85 – 7.65 m); [c] $PhSO_2$ (7.74 – 7.52 m); [d] PhO (7.22 – 6.85 m); [e] 2-NO_2PhO (8.05 – 7.58 m); [f] 3-NO_2PhO (7.72 – 7.51 m); [g] 4-NO_2PhO (8.22 – 7.81 m); [h] CH_3S (2.84 s); [i] CH_3SO_2 (3.19 s); [j] $CH_3CONHPhS$ (3.58 s, 9.66 s, 7.47 – 7.18 m); [k] 1-methyl-2-imidazolylthio (2.96 s, 7.01 s, 7.21 s); [l] 2-furfurylthio (4.34 s, 6.31 dd, 6.37 d, 7.45 d); [m] Et_2N (1.01 t, 3.35 q).

TABLE V
^{13}C NMR spectra (δ, ppm)

Compound	CH_3	C-2	C-3	C-4	C-5	C-6	C-7	CO	C-2′	C-3′	C-4′	C-5′
III	44.13	150.51	123.29	115.99	128.68	127.95	135.53	178.70	153.56	121.87	113.86	149.55
IV	43.71	149.56	121.64	113.65	153.84	127.44	140.81	177.67	152.94	122.73	114.60	150.13
V[a]	43.95	151.46	122.50	120.90	150.69	128.06	136.12	178.56	153.31	121.90	113.74	149.52
VI[b]	43.65	152.83[c]	119.43	120.71	152.39[c]	127.62	139.96	177.89	153.86	122.83	114.03	150.25
VII	43.84	150.21	123.07	115.93	137.22	127.39	135.98	184.08	144.66	136.68	129.45	137.22

[a] X = PhS 133.84 (C-1), 130.37 (C-2, C-6), 130.31 (C-3, C-5), 128.44 (C-4); [b] X = $PhSO_2$ 139.52 (C-1), 128.65 (C-2, C-6), 130.63 (C-3, C-5), 135.21 (C-4); [c] the assignment may be interchanged.

3 H (CH_3); 4.71 s, 2 H (CH_2); 7.66 d, 1 H (H-3'); 6.78 dd, 1 H (H-4'); 7.99 d, 1 H (H-5'); J(3',4') = 3.9 Hz, J(4',5') = 1.9 Hz, J(3',5') < 1 (unresolved). ^{13}C NMR spectrum: 42.29 (CH_3), 61.56 (CH_2), 177.76 (CO), 152.91 (C-2'), 121.93 (C-3'), 113.85 (C-4'), 149.82 (C-5').

2-(2-Thienyl)-2-oxoethyl methyl sulfone (II): yield 51%, m.p. 117 – 118 °C. For $C_7H_8O_3S_2$ (156.3) calculated: 41.16% C, 3.95% H, 31.40% S; found: 41.75% C, 3.99% H, 31.84% S. IR spectrum, cm^{-1}: 1 647 (C=O), 1 303 (asym. SO_2), 1 157 (sym. SO_2). UV spectrum, nm (log ε): 266 (3.06), 293 (2.98). ^{1}H NMR spectrum: 3.19 s, 3 H (CH_3); 4.87 s, 2 H (CH_2); 8.09 d, 1 H (H-3'); 7.33 dd, 1 H (H-4'); 8.17 d, 1 H (H-5'); J(3',4') = 3.9 Hz, J(4',5') = 4.8 Hz, J(3',5') = 1.4 Hz. ^{13}C NMR spectrum: 42.28 (CH_3), 62.09 (CH_2), 183.03 (CO), 144.53 (C-2'), 136.65 (C-3'), 129.70 (C-4'), 137.51 (C-5').

1-(5-X-2-Furyl)-2-methylsulfonyl-2-furoyl- and 2-Thienocarbonylethylenes

Condensation products III – VIII. A solution of titanium tetrachloride (0.1 mol) in dry tetrachloromethane (25 ml) was added under stirring to dry tetrahydrofuran (200 ml) at 0 °C. Then, the corresponding fural (0.05 mol) and the β-ketosulfone (0.05 mol) were added in succession, the temperature being held between –5 °C and –10 °C. After addition of pyridine (0.2 mol) in tetrahydrofuran (30 ml) the reaction mixture was stirred at 0 °C to –5 °C for 48 h and then decomposed with water (50 ml). The product was extracted with ether and the ethereal solution dried and concentrated. After standing for 2 – 4 days the crystalline material was collected and purified by crystallization from ethanol.

Substitution products IX – XVIII. A solution of compound *III* (0.03 mol) and the corresponding sodium phenoxide or secondary amine, or compound *IV* (0.03 mol) and the sulfur nucleophile (0.09 mol), in acetonitrile (20 ml) were stirred under reflux, the reaction being monitored by thin-layer chromatography. The reaction mixture was concentrated and the product was isolated by column chromatography on silica gel in benzene–ethyl acetate (3 : 1) and crystallized from ethanol.

TABLE VI
Mass spectra of some synthesized compounds

Compound	*m/z* (relative abundance[a])
III	344 / 346, $M^{+\cdot}$ / $M^{+\cdot}$ (0.01/0.01), 265 (100), 186 (61), 158 (8), 129 (8), 123 (17), 102 (14), 95 (25), 63 (15), 51 (10), 39 (19)
IV	311, $M^{+\cdot}$ (0.01), 265 (87), 186 (70), 158 (12), 130 (9), 123 (19), 95 (100), 76 (10), 63 (15), 51 (11), 39 (26)
V	374, $M^{+\cdot}$ (0.03), 265 (100), 202 (6), 186 (42), 123 (18), 110 (7), 102 (6), 95 (48), 77 (5), 51 (6), 39 (8)
VI	406, $M^{+\cdot}$ (0.001), 265 (100), 202 (6), 186 (43), 125 (6), 123 (18), 102 (7), 95 (55), 77 (9), 51 (8), 39 (8)
VII	360 / 362, $M^{+\cdot}$ / $M^{+\cdot}$ (0.01/0.01), 281 (100), 202 (52), 174 (13), 157 (5), 145 (14), 123 (24), 111 (86), 83 (11), 63 (13), 39 (25)

[a] The table lists relative abundances of both $M^{+\cdot}$ and 9 – 10 most intense peaks.

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