SYNTHESIS AND REACTIONS OF ALKYL 3-BROMOMETHYL-3-(2-FURYL)-2-PROPENOATES WITH SULFUR CONTAINING NUCLEOPHILES*

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Preparation and nucleophilic displacement reactions of alkyl 3-bromomethyl-3-(2-furyl)-2-propenoates with sulfur containing nucleophiles is described. The UV, IR and ^{1}H-NMR spectra of the synthesized compounds are interpreted.

This paper concerns the synthesis of compounds of furylethylene type with three and four substituents at the ethylene bond, which are derivatives and structural analogues of 3-(2-furyl)-2-propenoic acid, and their physicochemical and biological properties. The starting material for synthesis of derivatives of 3-X-methyl-3-(2-furyl)-propenoic acid was 3-bromomethyl-3-(2-furyl)-2-propenoic acid and its esters prepared by bromination of alkyl 3-methyl-3-(2-furyl)-2-propenoate under conditions of a selective radical bromination of the methyl at the double bond. Ethyl 3-methyl-3-(2-furyl)-2-propenoate was obtained from 2-acetylfuran and ethyl bromoacetate in a low yield and with many by-products[1]. Further 3-alkyl substituted derivatives of 3-(2-furyl)-2-propenoic acid were synthesized according to Horner's modification of Wittig reaction[2] in better yields, but in a more labourious way.

This paper deals with the preparation of alkyl 3-methyl-(2-furyl)-2-propenoates free of by-products by reacting diazomethane with alkyl 3-(2-furyl)-2-propenoate followed by a thermic decomposition of the pyrazoline formed. Bromination of alkyl 3-methyl-3-(2-furyl)-2-propenoates gave the corresponding 3-bromomethyl derivatives with two reactive centres utilizable for nucleophilic displacements. Moreover, nucleophilic displacements with sulfur containing reagents was also studied. The structure of products and the similarity of these reactions with those of S_N displacement of halogen derivatives of allylic type indicate that an S_N2 mechanism can be involved[3].

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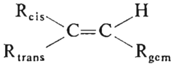
3-Mercaptomethyl-3-(2-furyl)-2-propenoic acid was attempted to prepare from the starting ester and thiourea analogously as 9-mercaptofluorene from 9-bromofluorene and thiourea; nonetheless, the desired compound could not be isolated. Upon acidification of the reaction mixture a crystalline product separated; the structure 4-(2-furyl)-3-thiolen-2-one was ascribed to it on the basis of spectral (IR, UV, ^{1}H-NMR and mass) evidence.

Constitution of all products was proved by IR, UV and of some of them also by ^{1}H-NMR spectra. Characteristic data of the obtained products are listed in Table I. The most significant band in the IR spectra belonged to stretching vibrations of the carbonyl group; in compounds *I–XXII* it is localized in the 1680 to 1716 cm^{-1} range[4]. The cyclization product *XXIV*, which is an α,β-unsaturated ketone, has this band at 1680 cm^{-1}. Bands ascribed to stretching vibrations of the ethylenic C=C and aromatic C=C bonds were observed in the 1626–1616 cm^{-1} range. A medium strong band at 1299–1221 cm^{-1} belongs to asymmetric vibrations of the C—O—C bond and a strong band at 1035–1025 cm^{-1} to symmetric vibrations of the same bond. The band at about 880 cm^{-1} was ascribed to the out-of-plane deformation vibrations of the furan ring (Table II). Two maxima were seen in the electronic absorption spectra: the first one in the 206–224 nm range belongs to the $\pi \rightarrow \pi^*$ electronic transition of the furan ring, the second in the 300–320 region is associated with the $\pi \rightarrow \pi^*$ electronic transition through the whole furylacrylic system (Table III, ref.[4,5]).

The positions of proton signals in the ^{1}H-NMR spectrum evidenced the starting ester of 3-bromomethyl-3-(2-furyl)-2-propenoic acid to be an *E*-isomer; the sulfur analogues, prepared by nucleophilic displacement of this ester, had the same geometry. Identification of *E*-isomers was based upon comparison of the calculated and found values of chemical shift of olefinic protons. Chemical shifts of olefinic protons for *E* and *Z*-isomers were calculated on the basis of additive increments for substituents R in equation[6,7]:

$$\delta C{=}CH = 5{\cdot}25 + Z_{gem} + Z_{cis} + Z_{trans}$$



$$(R_{cis})(R_{trans})C{=}C(H)(R_{gem}) .$$

Since increments for heterocyclic systems were not reported, we used increments of an aromatic ring for the furan skeleton. Table IV lists the ^{1}H-NMR spectral data of compounds *I–III*, *VI*, *VIII*, *XII*, *XV*, *XVI* and *XXIV*.

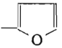
EXPERIMENTAL

The S_N reactions were effected with alkylthiols, arylthiols, arylsulfinates, C-alkyl dithiocarbonates, KSCN and thiourea.

TABLE I
Alkyl Esters of 3-X-Methyl-3-(2-furyl)-2-propenoic Acid

Compound	X R	Mol. formula (mol. weight)	B.p., °C/Pa m.p., °C (yield, %)	Calculated/Found		
				% C	% H	% S
I	Br C_2H_5	$C_{10}H_{11}BrO_3$ (259·1)	38–39 (71·4)	46·31 45·97	4·24 4·05	30·79[b] 30·61[b]
II	S—CH_3 C_2H_5	$C_{11}H_{14}O_3S$ (226·3)	111–112 (61·8)	58·32 58·02	6·18 6·03	14·15 13·97
III	S—C_2H_5 C_2H_5	$C_{12}H_{16}O_3$ (240·3)	78–80 (69·1)	59·92 59·70	6·65 6·40	13·30 13·26
IV[a]	S—C_3H_7 C_2H_5	$C_{13}H_{18}O_3S$ (254·3)	— (60·0)	61·34 61·01	7·07 7·01	12·58 12·48
V[a]	S-i-C_3H_7 C_2H_5	$C_{13}H_{18}O_3S$ (254·3)	— (48·3)	61·34 61·13	7·07 7·03	12·58 12·38
VI[a]	S—C_4H_9 C_2H_5	$C_{14}H_{20}O_3S$ (268·4)	— (56·2)	62·59 62·28	7·45 7·29	11·95 11·82
VII[a]	S-i-C_5H_{11} C_2H_5	$C_{15}H_{22}O_3S$ (282·4)	— (50·8)	63·73 63·60	7·79 7·80	11·33 10·99
VIII[a]	S—C_6H_{11} C_2H_5	$C_{16}H_{22}O_3S$ (294·4)	— (80·3)	65·21 65·03	7·47 7·38	10·97 11·04
IX	S—C_6H_5 CH_3	$C_{15}H_{14}O_3S$ (274·2)	62–69/6·5 (80·3)	65·69 65·43	5·10 5·01	11·67 11·81
X	S—$C_6H_4OCH_3$ CH_3	$C_{16}H_{16}O_4S$ (304·2)	73–78/5·2 (88·1)	63·15 62·95	5·26 5·03	10·52 10·33
XI	S—$C_6H_4NHCOCH_3$ CH_3	$C_{17}H_{17}NO_4S$ (331·2)	103–105 (61·4)	61·64 61·48	5·13 5·01	9·66 9·39
XII[a]	S—CH_2—C_6H_5 C_2H_5	$C_{17}H_{18}O_3S$ (302·4)	— (74·5)	67·46 67·26	5·95 5·70	10·58 10·65
XIII[a]	SO—C_4H_9 C_2H_5	$C_{14}H_{20}O_4S$ (284·4)	— (36·2)	59·07 58·91	7·03 6·65	11·25 11·06
XIV[a]	SO—C_6H_{11} C_2H_5	$C_{16}H_{22}O_4S$ (310·4)	— (46·3)	61·85 61·60	7·08 7·01	10·30 10·16
XV	SO_2—C_4H_9 C_2H_5	$C_{14}H_{20}O_5S$ (300·4)	65–66 (53·2)	55·92 55·73	6·65 6·52	10·65 10·38
XVI	SO_2—C_6H_{11} C_2H_5	$C_6H_{22}O_5S$ (326·4)	108–109 (64·3)	58·82 58·57	6·74 6·61	9·80 9·96
XVII	SO_2—C_6H_5 CH_3	$C_{15}H_{15}O_5S$ (306·1)	53–58/5·2 (58·9)	58·86 58·69	4·57 4·41	10·45 10·37

TABLE I
(*Continued*)

Com-pound	X R	Mol. formula (mol. weight)	B.p., °C/Pa m.p., °C (yield, %)	Calculated/Found		
				% C	% H	% S
XVIII	$SO_2—C_6H_4—CH_3$ CH_3	$C_{16}H_{16}O_5S$ (320·2)	109—110 (73·6)	60·00 59·83	4·99 4·87	9·99 9·79
XIX	SO_2—  CH_3	$C_{13}H_{12}O_6S$ (296·0)	79—85/5·2 (52·7)	52·74 52·38	4·05 3·98	10·81 10·70
XX	$S—CS—OCH_3$ CH_3	$C_{11}H_{12}O_4S_2$ (272·4)	104—106 (60·3)	48·55 48·01	4·40 4·21	23·49 23·38
XXI[a]	$S—CS—OC_2H_5$ CH_3	$C_{12}H_{14}O_4S_2$ (286·4)	— (58·3)	50·27 49·89	4·88 4·76	22·34 22·11
XXII[a]	$S—CS—O\text{-}i\text{-}C_3H_7$ CH_3	$C_{13}H_{16}O_4S_2$ (300·4)	— (55·4)	51·93 51·69	5·32 5·20	21·30 21·19
XXIII	SCN CH_3	$C_{10}H_9NO_3S$ (223·2)	68—72/5·2 (76·2)	53·81 53·59	4·03 3·98	14·34 14·41
XXIV[c]	— —	$C_8H_6O_2S$ (166·1)	103—105 (61·6)	57·85 57·71	3·61 3·58	19·26 19·12

[a] Chromatographically purified liquid tarred during measurement of physical constants, [b] % Br, [c] 4-(2-furyl)-3-thiolen-2-one.

4-(2-Furyl)-3-ethoxycarbonyl-2-pyrazoline

A mixture of ethereal solution of diazomethane (0·1 mol) and ethyl 3-(2-furyl)-2-propenoate (50 mmol) was allowed to stand at −10°C for some days. The separated product, which crystallized from chloroform, had m.p. 109—110°C.

Ethyl 3-Methyl-3-(2-furyl)-2-propenoate

4-(2-Furyl)-3-ethoxycarbonyl-2-pyrazoline (40 mmol) was heated at 220—230°C under nitrogen for 30 min. The product distilled under reduced pressure at 85—86°C/130 Pa.

Ethyl 3-Bromomethyl-3-(2-furyl)-2-propenoate

N-Bromosuccinimide (0·1 mol) and azo-bis-isobutyronitrile (2 mmol) were added to a solution of ethyl 3-methyl-3-(2-furyl)-2-propenoate (0·1 mol) in tetrachloromethane. After 4 h of heating under reflux the solution was cooled, the separated succinimide filtered off, tetrachloromethane distilled off and the residue distilled *in vacuo*. B.p. 92—95°C/30 Pa. This derivative strongly irritates the skin.

Esters of 3-X-Thiomethyl-3-(2-furyl)-2-propenoic Acid

Sodium alkylthiolate or arylthiolate (7 mmol) in ethanol (20 ml) was added to a solution of the ester of 3-bromomethyl-3-(2-furyl)-2-propenoic acid (5 mmol) and refluxed for 3 h. The mixture was then poured into water (50 ml) and the organic constituent extracted with ether (3 × 50 ml). The residue remaining after drying and concentration of the ethereal layer was purified either by vacuum distillation or column chromatography.

Esters of 3-Arylsulfomethyl-3-(2-furyl)-2-propenoic Acid

Sodium arylsulfinate (4·1 mmol) was hot-dissolved in dimethylformamide (5 ml) and an ester of 3-bromomethyl-3-(2-furyl)-2-propenoic acid (4·1 mmol) was added. The mixture was heated

TABLE II

Characteristic Infrared Spectral Data (cm^{-1})

Compound	δ(C—H)	ν_s(COC)	ν_{as}(COC)	ν(C=C)	ν(C=O)	Other vibrations
I	879	1 035	1 293	1 611, 1 441	1 713	—
II	880	1 034	1 298	1 611, 1 442	1 710	—
III	878	1 035	1 295	1 612, 1 444	1 712	—
IV	883	1 030	1 292	1 625, 1 448	1 711	—
V	882	1 030	1 290	1 625, 1 446	1 709	—
VI	884	1 028	1 290	1 624, 1 446	1 709	—
VII	883	1 029	1 282	1 620, 1 446	1 707	—
VIII	883	1 032	1 290	1 630, 1 450	1 707	—
IX	885	1 030	1 226	1 626, 1 484	1 710	—
X	885	1 026	1 231	1 624, 1 486	1 761	—
XI	884	1 025	1 229	1 623, 1 507	1 700	—
XII	883	1 030	1 290	1 624, 1 456	1 708	—
XIII	883	1 029	1 291	1 621, 1 624	1 712	1 058[a]
XIV	880	1 031	1 293	1 624	1 710	1 056[a]
XV	884	1 031	1 299	1 624	1 713	1 322[b,c]
XVI	882	1 032	1 295	1 622	1 713	1 317[b,d]
XVII	884	1 030	1 225	1 626, 1 482	1 699	1 320[b,e]
XVIII	885	1 031	1 227	1 616, 1 480	1 702	1 317[b,c]
XIX	883	1 029	1 221	1 625, 1 483	1 702	1 318[b,f]
XX	884	1 030	1 294	1 625	1 680	1 115[g]
XXI	882	1 027	1 296	1 626	1 685	1 112[g]
XXII	886	1 030	1 292	1 625	1 681	1 114[g]
XXIII	885	1 027	1 228	1 623, 1 480	1 701	2 156[h]
XXIV	885	1 031	1 258	1 628, 1 481	1 680	—

[a] ν(S—O); [b] $\nu_{as}(SO_2)$; [c] $\nu_s(SO_2)$, 1170 cm^{-1}; [d] $\nu_s(SO_2)$ 1165 cm^{-1}; [e] $\nu_s(SO_2)$ 1172 cm^{-1}; [f] $\nu_s(SO_2)$ 1169 cm^{-1}; [g] ν(C=S); [h] ν(SCN).

TABLE III

Bands Maxima of Electronic Absorption Spectra

Compound	λ_{max}, nm	log ε	λ_{max}, nm	log ε	Compound	λ_{max}, nm	log ε	λ_{max}, nm	log ε
I	224	3.69	320	4·20	*XIII*	212	4·01	309	4·26
II	209	3·96	316	4·26	*XIV*	218	4·16	307	4·27
III	221	4·07	329	4·24	*XV*	212	4·04	315	4·25
IV	212	4·19	311	4·23	*XVI*	215	3·99	314	4·23
V	213	4·16	306	4·24	*XVII*	221	4·07	315	4·26
VI	213	3·95	307	4·22	*XVIII*	222	4·19	316	4·28
VII	213	4·03	309	4·28	*XIX*	217	4·12	316	4·19
VIII	206	4·08	310	4·23	*XX*	220	3·84	314	4·24
IX	217	4·13	309	4·13	*XXI*	210	3·96	309	4·22
X	219	3·98	305	4·24	*XXII*	221	3·92	300	4·24
XI	220	3·99	305	4·21	*XXIII*	213	4·10	317	4·39
XII	214	4·13	309	4·16	*XXIV*	216	3·50	318	4·17

at 50°C for 2 h, cooled and poured onto ice (50 g). The product was the next day vacuum-distilled. Compound *XVII* was crystallized from methanol.

S-[2-(2-Furyl)-3-methoxycarbonyl-2-propenyl]-O-alkyldithio Carbamates

An ester of 3-bromomethyl-3-(2-furyl)-2-propenoic acid (50 mmol) was added to a solution of potassium O-alkyldithio carbamate (10 mmol) dissolved in acetone (30 ml) at a reflux temperature. After 3 h the mixture was cooled and poured into water (100 ml). The organic material was extracted with ether (3 × 50 ml), dried with sodium sulfate and thickened. The raw product was purified by column chromatography on alumina with solvent system chloroform–acetone 2 : 1.

Ethyl 3-Butyl and 3-Cyclohexylsulfinylmethyl-3-(2-furyl)-2-propenoates

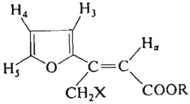
The title esters were obtained by oxidation of the corresponding sulfides. Ethyl 3-butyl or 3-cyclohexylthiomethyl-3-(2-furyl)-2-propenoate (3 mmol) was mixed with hydrogen peroxide (30%, 3 ml) in acetone (20 ml) and stirred for 30 min. After 24 h of standing at room temperature acetone was distilled off, ether added, the solution dried, concentrated and the raw product purified by chromatography on thin layer of silica gel with benzene–ethyl acetate 3 : 1 as solvent system.

Ethyl 3-Butyl and 3-Cyclohexylsulfomethyl-3-(2-furyl)-2-propenoates

These esters were prepared by oxidation of the corresponding sulfides. Ethyl 3-butyl or 3-cyclohexylthiomethyl-3-(2-furyl)-2-propenoates (3 mmol) was mixed with hydrogen peroxide (30%,

TABLE IV

Chemical Shifts (ppm)



Compound[a]	H$_\alpha$	H$_3$	H$_4$	H$_5$	=C—CH$_2$	R	
						CH$_2$	CH$_3$
I	6·36	6·78	6·45	7·44	4·86	4·23	1·30
II	6·62	6·89	6·56	7·50	4·91	4·26	1·31
III	6·61	6·90	6·50	7·48	4·88	4·21	1·38
VI	6·40	6·73	6·45	7·42	4·15	4·18	1·30
VIII	6·36	6·71	6·42	7·42	4·16	4·20	1·27
XII	6·39	6·53	6·37	7·38	4·11	4·18	1·26
XV	6·61	6·89	6·50	7·48	4·91	4·27	1·34
XVI	6·62	6·88	6·49	7·47	4·90	4·25	1·33
XXIV	6·55	6·81	6·55	7·56	4·32	—	—

[a] Calculated values[7] for $\delta_{C=CH}$: X = Br, *E*-isomer 6·35 ppm, *Z*-isomer 6·07 ppm; X = S-alkyl, *E*-isomer 6·17 ppm; *Z*-isomer 5·83 ppm.

3 ml) in 60% acetic acid. The mixture was stirred till the sulfide dissolved and then allowed to stand for 3 days. The separated sulfones were suction filtered and crystallized.

Methyl 3-Thiocyanatomethyl-3-(2-furyl)-2-propenoate

Methyl 3-bromomethyl-3-(2-furyl)-2-propenoate (4·1 mmol) in acetone (10 ml) was added to potassium thiocyanate (4·1 mmol) in water (1 ml) and refluxed for 2 h. The organic material was extracted after addition of water (20 ml) with benzene (4 × 50 ml). The organic layer was dried, concentrated and purified by column chromatography on alumina, chloroform–acetone 2 : 1 being the solvent system.

Spectral Measurements

The IR spectra were measured with a UR-20 (Zeiss, Jena) spectrometer in chloroform in a 0·26 mm-cell or in KBr discs at a 2 mg/1 g KBr concentration. The UV spectra were recorded with a UV VIS (Zeiss, Jena) apparatus in ethanol at a $5 . 10^{-5}$ mol/l concentration in a 10 mm-cell. The ^{1}H-NMR spectra were taken with a Tesla BS 487 C instrument operating at 80 MHz in deuteriochloroform, tetramethylsilane being the internal standard.

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