

STUDY OF THE STEREOCHEMICAL COURSE OF WITTIG-HORNER REACTION IN FURAN COMPOUNDS*M. ČERNAYOVÁ^a, J. KOVÁČ^a, M. DANDÁROVÁ^a, B. HASOVÁ^a and R. PALOVČÍK^b^a Department of Organic Chemistry,

Slovak Institute of Technology, 880 37 Bratislava and

^b Institute of Chemistry, Slovak Academy of Sciences, 809 33 Bratislava

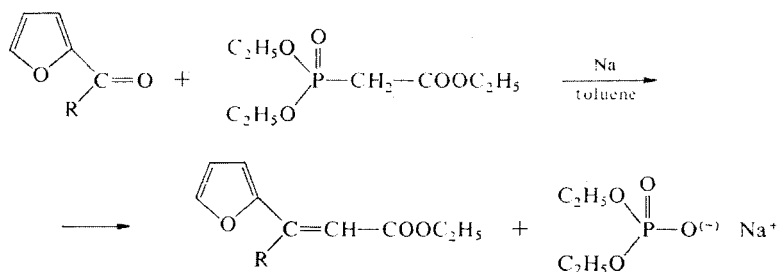
Received June 26th, 1975

Preparation of 3-R-substituted 2-furylacrylates, where R is CH₃, C₂H₅, n-C₃H₇, n-C₄H₉, i-C₄H₉, t-C₄H₉, n-C₅H₁₁, C₆H₅, 2-furyl, 2-pyrrolyl and 2-thienyl, by Horner modification of the Wittig synthesis is described. The stereochemistry of the arising alkyl derivatives and the effect of size and branching of the alkyl on the ratio of the *E* and *Z* isomers is investigated using gas-liquid chromatography and ¹H-NMR spectroscopy.

Only scarce data are available in the literature on derivatives of β-substituted furylacrylic acids. Ethyl 3-methyl-3-(2-furyl)acrylate¹, ethyl 3-phenyl-3-(5-nitro-2-furyl)acrylate² and also 3-substituted methyl furylacrylates, where the substituent (R) is 1-pyrrolidinyl, 2-piperazinyl and morpholinyl³, have already been prepared. β-Substituted furylacrylates can be prepared by condensation reactions of alkyl furyl ketones, the method of choice being the Horner modification of the Wittig reaction^{4,5} in which phosphonoacetates are condensed with aldehydes or ketones to give substituted acrylates. In contrast to other methods, leading to α,β-unsaturated esters, this method affords higher yields, the reaction is carried out under mild conditions and the product isolation is relatively simple⁶. Janovskaya and Kucherov⁷ studied the stereochemical course of the Wittig-Horner reaction. Reaction with aldehydes affords stereospecifically *E* isomer whereas dialkyl ketones give a mixture of *E* and *Z* isomers. The formation of isomers in the reaction of alkyl aryl ketones with triethyl α-phosphonopropionate is described also by Gallagher and Webb⁸. In the furan series, this method was used in the preparation of ethyl furylacrylate from furaldehyde in 71% yield⁶ but no comments on the stereochemistry of this reaction were given.

The objective of this study was the preparation of ethyl β-substituted furylacrylates by Wittig-Horner reaction of alkyl and aryl 2-furyl ketones with ethyl diethylphosphonoacetate according to Scheme 1.

* Part LXX in the series Furan Derivatives; Part LXIX: This Journal 41, 614 (1976).



R = alkyl, aryl

SCHEME 1

Alkyl and aryl 2-furyl ketones were prepared by acylation of furan, following procedures described in the literature⁹⁻¹¹. The acylation of furan with pivaloyl chloride in carbon disulphide afforded the hitherto not described tert-butyl 2-furyl ketone. Ethyl diethylphosphonoacetate was synthesised by a modification of Arbuzov reaction¹². The prepared β -substituted furylacrylates and their physical constants are listed in Table I. The yields of the reaction are 53–89% and they drop with increasing branching of the alkyl in the corresponding ketone.

Gas-chromatographic analyses and ¹H-NMR spectroscopy have shown that all the prepared β -substituted furylacrylates represent mixtures of *Z* and *E* isomers. These geometric isomers were separated by gas-liquid chromatography. Their gas-liquid chromatographic data and relative ratios in the mixture are given in Table I. The compounds were analysed by ¹H-NMR spectroscopy (Table II). The spectra exhibit two signals of different intensity which were assigned to the H _{α} protons in the *Z* and *E* isomers; these signals were used in the identification of the isomers and in the determination of their relative ratio. The chemical shifts of the olefinic protons in the isomers *E* and *Z* were calculated using additive increments for the substituents R in the *gem*, *cis* and *trans* position relative to the proton in question¹³:

$$\delta_{\text{C}=\text{CH}} = 5.25 + Z_{\text{gem}} + Z_{\text{cis}} + Z_{\text{trans}}$$

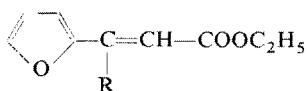
$$\begin{array}{c}
 \text{R}_{\text{cis}} \quad \text{H} \\
 \diagdown \quad \diagup \\
 \text{C}=\text{C} \\
 \diagup \quad \diagdown \\
 \text{R}_{\text{trans}} \quad \text{R}_{\text{gem}}
 \end{array}$$

Signals of the olefinic protons were assigned to *Z* and *E* isomers on the basis of comparison of the calculated and observed chemical shifts. The increments for the heterocyclic systems are not known¹³ and therefore for the furan ring we used the increments for an aromatic system. The calculated values of chemical shifts agree well with that found experimentally. The differences between the chemical shifts of the H _{α} proton signals for the *Z* and *E* isomers are sufficiently great (~ 0.6 p.p.m.)

to allow configurational assignment to the isomers. The ratio *Z* : *E* was determined from integrated intensities of the signals of the H_{α} olefinic protons in the corresponding isomers. The signals of the protons H_4 and H_5 of the furan ring in both isomers

TABLE I

Physical Properties and Gas-Liquid Chromatographic Data of β -Substituted Furylacrylates

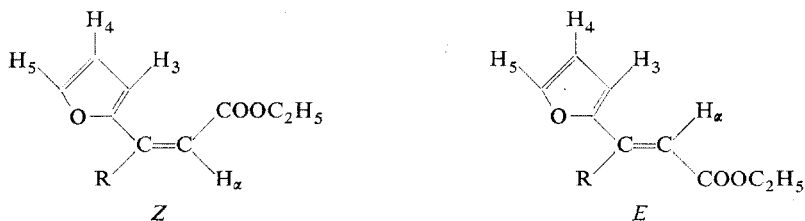


Compound R	Formula (mol.wt.)	B.p., °C/Torr (yield, %)	Calculated/Found		Ret. time, min		Ratio <i>Z</i> : <i>E</i>
			% C	% H	R_{1Z} R_{1E}		
<i>I</i>	—	85–86/1 ^a	—	—	12.76		0.6 : 1
CH ₃	—	(67)	—	—	14.32		
<i>II</i>	C ₁₁ H ₁₄ O ₃	88–94/1	68.03	7.26	14.61		2.0 : 1
C ₂ H ₅	(194.2)	(71)	67.81	7.23	15.20		
<i>III</i>	C ₁₂ H ₁₆ O ₃	97–101/2	69.24	7.74	17.06		2.7 : 1
n-C ₃ H ₇	(208.25)	(83)	68.96	7.59	18.00		
<i>IV</i>	C ₁₂ H ₁₆ O ₃	106–110/3	69.24	7.74	18.02		3.7 : 1
i-C ₃ H ₇	(208.25)	(69)	69.15	7.70	18.97		
<i>V</i>	C ₁₃ H ₁₈ O ₃	115–117/2	70.25	8.16	20.36		2.7 : 1
n-C ₄ H ₉	(222.3)	(81)	69.97	8.02	21.14		
<i>VI</i>	C ₁₃ H ₁₈ O ₃	112–115/3	70.25	8.16	21.50		3.8 : 1
i-C ₄ H ₉	(222.3)	(72)	70.13	8.10	22.17		
<i>VII</i>	C ₁₃ H ₁₈ O ₃	100–102/1	70.25	8.16	—		—
t-C ₄ H ₉	(222.3)	(53)	69.85	7.95	—		
<i>VIII</i>	C ₁₄ H ₂₀ O ₃	90–95/1	71.14	8.53	25.30		2.7 : 1
n-C ₅ H ₁₁	(236.3)	(66)	71.10	8.52	26.02		
<i>IX</i>	C ₁₅ H ₁₄ O ₃	128–130/1	74.22	5.81	—		—
phenyl	(242.3)	(71)	74.10	5.82	—		
<i>X</i>	C ₁₃ H ₁₂ O ₃ S	125–129/2	62.87	4.87	—		—
2-thienyl	(248.3)	(59)	62.70	4.86	—		
<i>XI</i>	C ₁₃ H ₁₃ O ₃ N	112–114/2	67.51	5.66	—		—
2-pyrrolyl	(231.2)	(61)	67.22	5.53	—		
<i>XII</i>	C ₁₃ H ₁₄ O ₂	120–123/1	67.25	5.21	—		—
2-furyl	(232.2)	(51)	67.05	5.18	—		

^a Ref. 1.

exhibit almost identical chemical shifts. The spectrum contains two signals of different intensity, which were attributed to the protons H_3 ; these exhibit different chemical shifts for the isomers Z and E (difference about 0.6 p.p.m.). The ratio of the integrated intensities of these signals is in accord with the ratio of the integrated intensities of the H_x olefinic proton signals in Z and E isomers. On the basis of these results it is possible to draw certain conclusions about the conformation of the furylvinyl system. The signal due to H_3 at lower field belongs to the Z isomer. The shift is caused by an anisotropic effect of the carbonyl group which is close to the proton H_3 . The obtained data show that the furylvinyl system in the Z -isomers of β -substituted furylacrylates has s' -*cis* conformation. For comparison, we may

TABLE II
 $^1\text{H-NMR}$ Data for β -Substituted Furylacrylates



Compound		H_x^a	H_3^a	H_4^a	H_5^a	Ratio $Z : E$
I	<i>Z</i>	5.73 q	7.31 dd	6.41 dd	7.41 dd	0.6 : 1
	<i>E</i>	6.36 q	6.62 dd	6.41 dd		
II	<i>Z</i>	5.73 t	7.20 dd	6.44 dd	7.42 bd	1.7 : 1
	<i>E</i>	6.31 bs	6.63 bd	6.43 dd		
III	<i>Z</i>	5.72 t	7.22 dd	6.41 dd	7.40 bd	2.5 : 1
	<i>E</i>	6.36 bs	6.62 bd	6.40 dd		
IV	<i>Z</i>	5.75 d	6.88 dd	6.41 dd	7.42 bd	4.0 : 1
	<i>E</i>	6.26 bs	6.66 bd	6.41 bd		
V	<i>Z</i>	5.71 t	7.23 dd	6.43 dd	7.41 bd	2.7 : 1
	<i>E</i>	6.30 bs	6.64 bd	6.42 dd		
VI	<i>Z</i>	5.62 t	7.15 dd	6.41 dd	7.33 bd	4.0 : 1
	<i>E</i>	6.30 bs	6.53 bd	6.41 dd		
VIII	<i>Z</i>	5.71 t	7.25 dd	6.43 dd	7.43 bd	2.7 : 1
	<i>E</i>	6.29 bs	6.64 bd	6.43 dd		

^a Chemical shifts given in δ (p.p.m.); s singlet, d doublet, t triplet, q quartet, b broad; calculated values¹³ for $\delta_{\text{C}=\text{CH}}$: *E*-isomer 6.13 p.p.m., *Z*-isomer 5.76 p.p.m.

mention that, according to X-ray study¹⁴ and ¹H-NMR spectroscopy¹⁵, the *trans*-furylacrylic acid exists in the *s'-trans* conformation. A certain anomaly is observed in the spectrum of the *Z*-isomer of β -isopropylfurylacrylate for which the chemical shift of the H₃ proton is lower than the shifts in other derivatives. This fact indicates a greater deviation from planarity of the system, caused by rotation of the furan nucleus from the plane of the conjugated system which lowers the deshielding effect of the carbonyl group.

The found *Z* : *E* ratios in the β -substituted furylacrylates show that the character of the alkyl group has a marked effect on the resulting isomer composition (Table I and II). In the compound *I* the *E* isomer predominates over *Z* isomer. The relative amount of *Z* isomer increases with the length and branching of the alkyl chain. Good agreement was found between the results of gas-liquid chromatographic and ¹H-NMR spectroscopic determinations of the *Z* : *E* ratio.

EXPERIMENTAL

Methods

The separation of *Z* and *E* isomers was carried out on a Hewlett-Packard 7620 A gas-liquid chromatograph equipped with flame-ionisation detector, using 8 ft columns packed with 10% UCW-98. The elution was programmed in two steps. Nitrogen flow rate 35 l/min, temperature of the injection chamber and flame-ionisation detector 250°C. The chromatograms were evaluated by an 9810 A integrator-calculator system, connected directly to the chromatograph. ¹H-NMR spectra were measured on a 80 MHz Tesla BS-487C spectrometer in 15% solutions in CDCl₃ at 25°C with tetramethylsilane as internal standard.

Tert-butyl 2-Furyl Ketone

Pivaloyl chloride (12 g; 0.1 mol) was added dropwise to anhydrous aluminium chloride (13.3 g; 0.1 mol) in carbon disulphide (120 ml) at 0°C under stirring. Then furan (6.8 g; 0.1 mol) in carbon disulphide (20 ml) was added during 20 minutes to the stirred mixture which turned gradually dark and liberated hydrogen chloride. After stirring for 30 minutes under cooling and for another 30 minutes at room temperature, the mixture was poured on ice (300 g), neutralised with 10% KOH and extracted with ether. The ethereal layer was dried over sodium sulphate, the solvent was evaporated and the residue distilled, affording 9.1 g (50.5%) of tert-butyl 2-furyl ketone, b.p. 63–65°C/1 Torr. For C₉H₁₂O₂ (142.2) calculated: 71.68% C, 7.95% H; found: 71.83% C, 7.85% H.

Ethyl Diethylphosphonoacetate

Diethyl phosphite (138 g; 1 mol), followed by ethyl chloroacetate (150 g; 1.2 mol), was added dropwise to a suspension of sodium (23 g; 1 mol) in *n*-hexane (500 ml). The resulting mixture was refluxed under stirring for 3 hours and set aside overnight. The colloidal sodium chloride was filtered off, the filtrate was taken down and the residue distilled, affording 141 g (63%) of the product, boiling at 154–155°C/2 Torr.

β -Substituted Furylacrylates

Ethyl diethylphosphonoacetate (0.05 mol) was added dropwise under stirring to finely cut sodium (0.05 g atom) in toluene (40 ml). The temperature rised to 40°C. The clear solution was cooled to 20°C and a solution of the corresponding ketone (0.045 mol) in toluene (20 ml) was added. The temperature rose to 30–33°C and the mixture was stirred on a water bath for 3 hours, cooled to 20°C, poured on ice and extracted with benzene (3 × 100 ml). The organic layer was dried over sodium sulphate, taken down and the product was distilled *in vacuo*. The yields and boiling points are given in Table I.

REFERENCES

1. Seiwerth R., Orescanin-Majhofer B.: *Ark. Kemi* 24, 53 (1952); *Chem. Abstr.* 49, 295 (1955).
2. Yoshina Shigetaka, Tanaka Akira, Guan Nan-Yang: *Yakugaku Zasshi* 88, 977 (1969); *Chem. Abstr.* 70, 3677 (1969).
3. Sasaki Tadashi, Shoji Katsuhiko: *Kagaku Nyokai Shi* 26, 264 (1968); *Chem. Abstr.* 69, 86721 (1968).
4. Horner L., Hoffmann H., Wippel H. G.: *Chem. Ber.* 91, 61 (1958).
5. Wadsworth W. S., Emmons W. D.: *J. Amer. Chem. Soc.* 83, 1733 (1961).
6. Tolochko A. F., Dombrovskij A. V.: *Ukr. Khim. Zh.* 31, 220 (1965).
7. Janovskaya L. A., Kucherov V. F.: *Izv. Akad. Nauk* 1964, 1341.
8. Gallagher G., Webb R. L.: *Synthesis* 1974, 122.
9. Hartough H. D., Kosak A. I.: *J. Amer. Chem. Soc.* 69, 3093 (1947).
10. Gilman H., Calloway N. D.: *J. Amer. Chem. Soc.* 55, 4197 (1933).
11. Šrogl J., Janda M., Stibor I.: *This Journal* 35, 3478 (1972).
12. Kosolapoff M. G.: *J. Amer. Chem. Soc.* 68, 1103 (1946).
13. Matter V. E., Pascual C., Pretsch E., Pross A., Simon W., Sternhell S.: *Tetrahedron* 25, 691 (1969).
14. Leiserowitz L., Rabinovich D.: *J. Chem. Soc. A* 1969, 2367.
15. Huckerby T. N.: *Tetrahedron Lett.* 1971, 353.

Translated by M. Tichý.