

STEREOCHEMICAL COURSE OF KNOEVENAGEL CONDENSATION OF FURAN COMPOUNDS*

†M. ČERNAYOVÁ, J. KOVÁČ, M. DANDÁROVÁ and O. RAJNIAKOVÁ

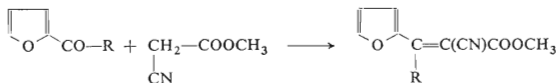
Department of Organic Chemistry,

Slovak Institute of Technology, 880 37 Bratislava

Received April 22nd, 1976

2-Cyano-3-R-3-(2-furyl)acrylates, where R is CH₃, C₂H₅, n-C₃H₇, i-C₃H₇, n-C₄H₉, i-C₄H₉, phenyl or thienyl, were prepared by the Cope modification of Knoevenagel condensation. Stereochemistry of this reaction was studied using ¹H-NMR spectroscopy and gas-liquid chromatography. Synthesis of model compounds and photoisomerisation of some of the *E*-isomers is described.

The Knoevenagel condensation of aromatic aldehydes with cyanoacetates proceeds stereospecifically under formation of *E*-isomers¹. Condensation of unsymmetrical ketones gives a mixture of *E* and *Z* isomers in which the isomer with *trans*-relation between the more bulky substituent and the carbalkoxy group predominates^{2,3}. In our previous paper⁴ we described the synthesis of 2-cyano-3-R-3-(2-furyl)acrylates by Cope modification of Knoevenagel condensation, together with the results of kinetic study of this reaction. The aim of the present investigation is to study the stereochemical course of this condensation (Scheme 1) and to determine the effect of alkyl or aryl groups in the starting ketones on the configuration of the arising products.



The stereochemistry of the products was studied by ¹H-NMR spectroscopy and gas-liquid chromatography. The model compounds IX–XIII were prepared by reaction of alkyl 2-furyl ketones with malononitrile or cyanoacetic acid under conditions given for the Cope modification of the Knoevenagel condensation. Physical constants of the compounds IX–XIII are given in Table I. Reaction of acetylfuran with cyanoacetic acid afforded after 12 h the condensation product IX, together with the decarboxylation product X. Condensation of n-propyl 2-furyl ketone with cyano-

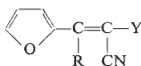
* Part LXXXI in the series Furan Derivatives; Part LXXX: This Journal 42, 338 (1977).

acetic acid afforded after 2 hours 22% of the free acid *XIII*, in accord with the literature⁵. 3-Methyl-3-(2-furyl)acrylonitrile (*X*) was prepared also by decarboxylation of 2-cyano-3-methyl-3-(2-furyl)-acrylic acid (*IX*) in pyridine.

The reaction affords two stereoisomers, *E* and *Z*, as shown by ¹H-NMR spectroscopic and gas-liquid chromatographic study of the compounds *I*–*VIII*. The pertinent data are given in Table II. Table III shows ¹H-NMR data of the model compounds *IX*–*XI*. The geometric configuration was assigned to the isomers on the basis of chemical shifts of the protons in the substituent R (methyl, methylene or methine group). We made use of the finding of Hayshi and coworkers^{2,3} that in esters of 3-methyl substituted α,β -unsaturated acids the signals of the 3-methyl proton are situated at lower magnetic field in the *E*-isomer than in the *Z*-isomer. The difference between the chemical shifts in the *E*- and *Z*-isomers of methyl 3-methyl-3-(2-furyl)acrylate (*I*) was calculated from the difference between the chemical shifts of the methyl group in the position 3 for the *E* and *Z* isomers of 3-methyl-3-(2-furyl)acrylates (0.25 ppm) and from the magnitude of the deshielding effect on the

TABLE I

Physical Constants of 2-Y-3-R-3-(2-Furyl)acrylonitriles



Compound R Y	Formula (m.w.)	M.p., °C b.p., °C/Torr (yield, %)	Calculated/Found			λ_{\max} , nm (log ϵ)	$\nu(\text{CN})$, cm^{-1}
			% C	% H	% N		
<i>IX</i> CH ₃ COOH	C ₉ H ₇ NO ₃ (177.1)	118–119 (14.1) ^a	61.03 59.83	3.96 3.90	7.91 7.93	327 (4.199)	2 220
<i>X</i> CH ₃ H	C ₈ H ₇ NO (133.1)	78–79/1 (72.2) ^b	72.23 72.03	5.26 5.33	10.53 10.36	302 (4.393)	2 220 2 260
<i>XI</i> CH ₃ CN	C ₉ H ₆ N ₂ O (158.2)	80–81 (86.1)	68.21 68.05	3.82 4.01	17.68 17.94	342 (4.700)	2 235
<i>XII</i> C ₂ H ₅ H	C ₉ H ₉ NO (147.2)	93–95/1 (45.1)	73.47 73.47	6.16 6.12	9.52 9.33	300 (4.323)	2 218 2 258
<i>XIII</i> C ₃ H ₇ COOH	C ₁₁ H ₁₁ NO ₃ (205.2)	131–132 (22.6)	64.37 64.23	5.40 5.35	6.83 6.59	313 (2.560)	2 220

^a The reaction gives also the compound *X* (31.4%); ^b yield of the decarboxylation of the compound *IX*.

TABLE II

 Chemical Shifts (δ values, p.p.m.) of the Protons in Methyl 2-Cyano-3-R-3-(2-furyl)acrylates

Compound R	Iso-mer	R^a		$H_{3'}$	$H_{4'}$	$H_{5'}$	COOCH ₃	$E:Z^c$ ($E:Z$) ^d	R_{IE}^e R_{IZ}
		$C_{(1)}$	$C_{(2)}$						
I CH ₃	E	2.68	0.16	7.55	6.62	7.69	3.85	5.0:1	7.19
	Z	2.52	—	7.27	6.55	7.57	3.85	(5.0:1)	6.42
II C ₂ H ₅	E	3.16	0.26	7.54	6.62	7.68	3.84	3.6:1	7.72
	Z	2.90	—	7.25	6.57	7.59	3.84	(3.6:1)	6.77
III n-C ₃ H ₇	E	3.13	0.27	7.54	6.61	7.68	3.83	3.2:1	10.39
	Z	2.86	—	7.22	6.54	7.57	3.79	(3.4:1)	9.15
IV i-C ₃ H ₇	E	4.16	0.74	7.36	6.57	7.63	3.84	1.2:1	7.77
	Z	3.42	—	6.83	6.51	7.55	3.76	(1.1:1)	6.89
V n-C ₄ H ₉	E	3.12	0.29	7.55	6.62	7.71	3.83	3.5:1	14.37
	Z	2.83	—	7.22	6.55	7.58	3.77	(3.4:1)	12.60
VI i-C ₄ H ₉	E	3.13	0.38	7.55	6.62	7.69	3.84	2.5:1	11.70
	Z	2.75	—	7.14	6.55	7.57	3.78	(2.6:1)	10.38
VII phenyl	E	(7.12-7.56) ^g	—	6.65	6.54	7.73	3.64	2.5:1 ^h	13.08
	Z	(7.12-7.56)	—	—	—	—	3.88	—	—
VIII 2-thienyl	E	(7.77-7.19)	7.68 ^j	6.76	6.58	7.62	3.83	2.2:1 ^h	10.54
	Z	—	—	6.89	6.58	7.74	3.71	—	—

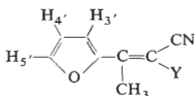
^a Chemical shifts of the protons bonded to $C_{(1)}$ and $C_{(2)}$ of the group R; ^b difference between the chemical shifts of the protons at $C_{(1)}$ of the group R in *E*- and *Z*-isomers; ^c determined from integrated signals of protons at $C_{(1)}$ or $H_{3'}$; ^d determined by gas-liquid chromatography; ^e retention time (min); ^f multiplet of the CH₂ protons; ^g multiplet of aromatic protons; ^h determined from signals of the protons of the methoxy-carbonyl group; ^j protons $H_{(3)}$, $H_{(4)}$ and $H_{(5)}$ in the 2-thienyl substituent.

protons in the β -methyl group caused by the cyano group (0.08 ppm; compound *X*, Table III). The calculated deshielding value of the methyl protons in the position 3 is 0.17 ppm, the found value is 0.16 ppm (Table II). For derivatives with a longer alkyl in the position 3 (compounds *III–VI*) the separation of signals of the more distant methyl groups is smaller. The chemical shifts of the protons of the alkoxy-carbonyl group in compounds *I* and *II* are identical for both isomers. Introduction of a more bulky substituent into the position 3 (compounds *III–VI*) results in a greater difference between the shifts of these signals in the particular isomers. The largest difference was observed in the case of the phenyl derivative (compound *VII*). The signals of the furan protons $H_{4'}$ and $H_{5'}$ in both isomers exhibit small differences in the chemical shifts. The greater separation of the $H_{3'}$ proton signals is caused by a different anisotropic effect of the carbonyl and cyano groups.

Besides comparison with the model compounds *IX–XI*, the correctness of assignment of the signals to the stereoisomers of cyano esters *I–VIII* was proved by comparison of the *E*- and *Z*-isomers which were obtained by irradiation of the pure isomers of the derivatives *I* and *II* in tetrachloromethane using a mercury lamp. Pure *E*-isomers were obtained by several crystallisations of the reaction mixture. According to $^1\text{H-NMR}$ analysis, irradiation of *I* afforded the *E*- and *Z*-isomers in the ratio 2 : 1 for *I* and 1.7 : 1 for *II*.

The $^1\text{H-NMR}$ spectra (Table III) show that decarboxylation of (*E*)-2-cyano-3-methyl-3-(2-furyl)acrylic acid (*IX*) in pyridine gave (*E*)- and (*Z*)-3-methyl-3-(2-

TABLE III
Chemical Shifts (δ values, p.p.m.) of the Protons in 3-Y-3-Methyl-3-(2-furyl)acrylonitriles



Compound Y	3-CH ₃	H _{3'}	H _{4'}	H _{5'}	H ₂	<i>E</i> : <i>Z</i>
<i>IX</i> COOH	<i>E</i> 2.65	7.58	6.75	7.91	—	—
<i>X</i> H	<i>E</i> 2.25 <i>Z</i> 2.17	6.65 7.03	6.46 6.46	7.43 7.43	5.67 5.10	1; 5.6
<i>XI</i> CN	—2.56	7.47	6.69	7.76	—	—

-furyl)-acrylonitrile (*X*) in the ratio 1 : 5.6. The configuration was assigned to the isomers on the basis of comparison of the calculated and found chemical shift of the olefinic proton^{6,7}.

As follows from the above results, the Knoevenagel condensation of alkyl and aryl 2-furyl ketones with methyl cyanoacetate affords a mixture of *E*- and *Z*-isomers in which the former isomer predominates. The effect of the length of the hydrocarbon chain is smaller than the effect of branching (the number of carbon atoms in the chain being the same). The reaction of aryl 2-furyl ketones results in the ratio *E* : *Z* = 2 : 1.

EXPERIMENTAL

Esters of 2-cyano-3-*R*-3-(2-furyl)acrylic acids were prepared by the Cope modification of the Knoevenagel condensation⁴. The IR spectra of 2-*Y*-3-*R*-3-(2-furyl)acrylonitriles were measured on a double-beam spectrophotometer UR-20 in 0.025M chloroform solutions. The UV spectra were obtained on a UV VIS Zeiss spectrophotometer in dioxane solutions, concentration 3–5 · 10⁻⁵M. ¹H-NMR spectra were taken at 25°C on a 80 MHz Tesla BS 4870 instrument in CDCl₃, using tetramethylsilane as internal standard. The isomers were separated by preparative gas-liquid chromatography on a Hewlett-Packard 7810 chromatograph with a flame-ionisation detector; 1.8 m column packed with 10% UCW 98 on Chromosorb (80–100 mesh). The temperature of the inlet chamber and of the detector was 230°C; column temperature 190°C, in the case of derivatives *VII* and *VIII* 220°C. Nitrogen flow rate 40 ml/min.

2-*Y*-3-*R*-(2-Furyl)acrylonitriles (*IX*–*XIII*)

A mixture of alkyl 2-furyl ketone (0.1 mol), cyanoacetic acid (17 g; 0.2 mol) or malonitrile (13.2 g; 0.2 mol), ammonium acetate (10 g) and glacial acetic acid (10 ml) in benzene was heated for 2–12 hours and water was removed azeotropically. The mixture was cooled, washed with 10% sodium carbonate solution (100 ml) and with water. The organic layer was dried and distilled. The physical constants of the products are given in Table I.

Decarboxylation of 2-Cyano-3-methyl-3-(2-furyl)acrylic Acid (*IX*)

A mixture of 2-cyano-3-methyl-3-(2-furyl)acrylic acid (1.8 g; 0.01 mol), copper powder (0.4 g; 0.006 mol) and pyridine (30 ml) was heated to 110°C for 10 hours. The copper and pyridine were removed from the reaction mixture and the residue was purified chromatographically on an alumina column, affording 0.95 g (72%) of 3-methyl-3-(2-furyl)acrylonitrile (*X*).

Photoisomerisation

A stirred solution of methyl (*E*)-2-cyano-3-methyl-3-(2-furyl)acrylate (0.95g; 0.005 mol) or methyl (*E*)-2-cyano-3-ethyl-3-(2-furyl)acrylate (1 g; 0.005 mol) in tetrachloromethane (60 ml) was irradiated using a mercury lamp (120 W) till the mixture began to darken (50 hours). The solvent was distilled off and the resulting mixture of *E*- and *Z*-isomer was studied by ¹H-NMR spectroscopy; (*E* : *Z*)_{CH₃} = 2 : 1, (*E* : *Z*)_{C₂H₅} = 1.7 : 1.

REFERENCES

1. Baker W., Howes C. S.: *J. Chem. Soc.* 1953, 119.
2. Hayashi T.: *J. Org. Chem.* 31, 3252 (1966).
3. Hayashi T., Igarashi M., Hayashi S., Midorikava H.: *Bull. Chem. Soc. Jap.* 38, 2063 (1965).
4. Černayová M., Kováč J., Surá J.: *This Journal*, in press.
5. Wittig G., Hartmann H.: *Chem. Ber.* 72, 1387 (1939).
6. Černayová M., Kováč J., Dandárová M., Hasová B., Palovčík R.: *This Journal* 41, 764 (1976).
7. Jackman L. M., Willey R. H.: *J. Chem. Soc.* 1960, 2886.
8. Matter U. E., Pacsual C., Presch E., Pross A., Simon W., Sternhell S.: *Tetrahedron* 25, 691 (1969).

Translated by M. Tichý.