

CONDENSATION OF 2-FURYL ALKYL KETONES
AND 2-FURYL ARYL KETONES
WITH SUBSTANCES HAVING AN ACTIVE METHYLENE GROUP*

† M. ČERNAYOVÁ, J. KOVÁČ and † J. SURÁ

*Department of Organic Chemistry,
Slovak Institute of Technology, 880 37 Bratislava*

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Methyl α -cyano- β -X-furylacrylates were prepared by reaction of 2-furyl alkyl ketones (alkyl = CH_3 , C_2H_5 , $n\text{-C}_3\text{H}_7$, $i\text{-C}_3\text{H}_7$, $n\text{-C}_4\text{H}_9$, $i\text{-C}_4\text{H}_9$) or 2-furyl aryl ketones (aryl = phenyl, 2-thienyl) with methyl cyanoacetate. The kinetics of their formation and the effect of bulkiness and branching of the alkyl group was investigated. The activation energy of methyl β -methylfurylacrylate and β -isopropylfurylacrylate formation was compared with that of 2-furylaldehyde upon reaction with methyl cyanoacetate.

The Cope modification¹ of Knoevenagel condensation, at which water formed during this reaction was azeotropically distilled off, proceeded with simple ketones in good yields. Steric conditions and reactivity of the carbonyl group play a prominent role also with this modification. Condensations with branched aliphatic ketones give low², with a heterocyclic ring possessing ketones even lower yields³ (e.g. phenyl 2-thienyl ketone - 8.8%). Another modification of Knoevenagel reaction was reported by Lehnert⁴, who employed a pre-prepared carbanion of the methylene component and catalytical amounts of TiCl_4 and pyridine for condensation of some ketones at a low temperature.

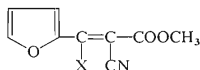
In this paper we wish to report a hitherto not described condensation of ketones of the furan series with methyl cyanoacetate. We examined the reaction kinetics and compared the reactivity of ketones under study with that of 2-furaldehyde.

Alkyl and aryl 2-furyl ketones were reacted in benzene in the presence of catalytical amounts of ammonium acetate; the water formed was azeotropically distilled off. Physical constants of compounds thus prepared are listed in Table I. Although the condensation was continued till water was formed (8-24 h) the yield of the reaction dropped with the increase and branching of the methyl group used. Tert-butyl 2-furyl ketone was not succeeded to condense nor at a higher temperature (in toluene or dimethylformamide). The condensation of aryl 2-furyl ketones proceeded under these reaction conditions with phenyl 2-furyl ketone only; with 2-thienyl or 2-pyrrolyl

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2-furyl ketone even the more reactive methylene component, *e.g.* malonic acid dinitrile, did not react. The condensation of 2-furyl 2-thienyl ketone was performable by the Lehnert's modification of Knoevenagel condensation in tetrahydrofuran at 0–5°C and 48 h. The carbanion added to the reaction mixture was pre-prepared by a reaction of sodium hydride and methyl cyanoacetate in tetrahydrofuran. The yield of methyl α -cyano- β -(2-thienyl)furylacrylate was 60.8%. The condensation of 2-pyrrolyl 2-furyl ketone did not take place under these conditions since the carbanion of the methylene component reacted preferentially with the hydrogen of pyrrole.

TABLE I
Physical Constants of Methyl α -Cyano- β -furylacrylates



Compound X	Formula	M.p., °C or B.p., °C/kPa (yield, %)	Calculated/Found			λ_{\max} , nm (log ϵ)	$\nu(\text{CN})$ (cm^{-1})
			% C	% H	% N		
<i>I</i> H	C ₉ H ₇ NO ₃ (177.1)	91–92 ^a (85.7)	—	—	—	337 (4.376)	2 230
<i>II</i> CH ₃	C ₁₀ H ₉ NO ₃ (191.2)	84–86 (73.5)	62.81 62.62	4.73 4.62	7.32 7.41	336 (4.408)	2 226
<i>III</i> C ₂ H ₅	C ₁₁ H ₁₁ NO ₃ (205.2)	64–65 (49.7)	64.37 64.31	5.39 5.29	6.67 5.59	337 (4.214)	2 220
<i>IV</i> n-C ₃ H ₇	C ₁₂ H ₁₃ NO ₃ (219.2)	101–102/0.3 (37.1)	65.75 65.59	5.98 5.85	6.39 6.21	336 (4.354)	2 228
<i>V</i> i-C ₃ H ₇	C ₁₂ H ₁₃ NO ₃ (219.2)	94–95/0.2 (35.6)	65.75 65.62	5.98 5.88	6.39 6.13	337 (4.150)	2 220
<i>VI</i> n-C ₄ H ₉	C ₁₃ H ₁₅ NO ₃ (233.2)	124–126/0.3 (40.7)	66.92 66.78	6.48 6.42	6.00 5.79	335 (4.255)	2 221
<i>VII</i> i-C ₄ H ₉	C ₁₃ H ₁₅ NO ₃ (233.2)	138–140/0.4 (40.1)	66.92 66.98	6.48 6.39	6.00 5.85	336 (4.240)	2 224
<i>VIII</i> C ₆ H ₅	C ₁₅ H ₁₁ NO ₃ (253.2)	160–162/0.3 (59.8)	71.15 71.01	4.38 4.24	5.53 5.30	336 (4.230)	2 220
<i>IX</i> 2-Thienyl	C ₁₃ H ₉ NO ₃ S (259.3)	86–88 (60.8)	—	—	5.39 ^b 5.20	346 (4.233)	2 217

^a Reference⁷; ^b calculated: 12.35% S; found: 12.07% S.

The kinetics of the Cope modification of Knoevenagel condensation was studied spectrophotometrically in the region of its characteristic UV-absorption band. The condensation was carried out in the presence of a catalytical amount of ammonium acetate in dioxane at 80°C under conditions of a pseudomolecular reaction. Table II lists the values of rate constants k , and half-lives $t_{1/2}$ of the reaction of 2-furyl alkyl ketones with methyl cyanoacetate and also the value of the rate constant of this reaction with 2-furaldehyde under the above-mentioned conditions. As seen, the condensation with ketones of the furan series is by 80 times slower than that of 2-furaldehyde. The rate constants obtained for the reaction with alkyl 2-furyl ketones correlate with the Taft's σ^* constants⁵ as evidenced by the linear relationship between $\log k$ and σ^* ($r = 0.9931$; $\rho = 2.85$). The extension and branching of the hydrocarbon chain results, as presumed, in the lowering of the condensation rate. The reaction with tert-butyl 2-furyl ketone does not occur at a measurable rate nor at a prolonged reaction time, increased temperature and a greater concentration gradient. The condensation of aryl 2-furyl ketones, where aryl was phenyl, 2-thienyl, 2-pyrrolyl proceeded by 10 times slower with phenyl 2-furyl ketone than that of the slowest reacting isobutyl 2-furyl ketone. Those 2-furyl ketones, where also the second component is a five-membered heterocyclic compound, do not enter the condensation under these reaction conditions. The Knoevenagel condensation with these ketones did not take place nor with malonic acid dinitrile.

To compare the reactivity of ketones derived from furan the activation energy value E was determined for the condensation of acetyl-2-furan and isopropyl 2-furyl ketone with methyl cyanoacetate. The value E was found to be 84.1 kJ . mol⁻¹ for

TABLE II
Kinetic Data of the Condensation of Alkyl 2-Furyl Ketones with Methyl Cyanoacetate at 80°C

Compound	X	σ^{*a}	$k \cdot 10^3$ l . mol ⁻¹ . min ⁻¹	$t_{1/2}$ min
I	H	0.490	154.60	4.98
II	CH ₃	0.000	6.36	57
III	C ₂ H ₅	-0.100	3.14	115
IV	n-C ₃ H ₇	-0.115	2.57	140
V	i-C ₃ H ₇	-0.190	3.05	119
VI	n-C ₄ H ₉	-0.130	2.96	122
VII	i-C ₄ H ₉	-0.125	2.15	169
VIII	phenyl	0.600	0.91	395

^a Reference⁵.

the former and $104.5 \text{ kJ} \cdot \text{mol}^{-1}$ for the latter, indicating thus the higher energy barrier when compared with that of 2-furaldehyde ($E = 62.4 \text{ kJ} \cdot \text{mol}^{-1}$).

EXPERIMENTAL

Alkyl 2-furyl ketones and aryl 2-furyl ketones were prepared by Friedel-Crafts reaction of furan derivatives⁶. The infrared spectra were measured with a double-beam UR-20 spectrometer in a 1.04 mm cell in chloroform at a 0.025M concentration. The apparatus was calibrated against a polystyrene foil; reading accuracy $\pm 1 \text{ cm}^{-1}$.

Methyl α -Cyano- β -alkyl-2-furylacrylates

A mixture consisting of alkyl 2-furyl ketone or aryl 2-furyl ketone (0.1 mol), methyl cyanoacetate (19.8 g, 0.2 mol), ammonium acetate (10 g) and glacial acetic acid (10 ml) was refluxed in benzene till the amount of water removed by azeotropic distillation did not increase (8–24 h). The reaction was then discontinued, the mixture cooled, washed with 10% solution of sodium carbonate (100 ml), water, dried with sodium sulphate and the solvent was distilled off. The product was purified by crystallization from ethanol or by distillation under reduced pressure. Physical constants of α -cyano- β -X-furylacrylates are listed in Table I.

Methyl α -Cyano- β -(2-thienyl)-furylacrylate

A solution of TiCl_4 (2.2 ml) in tetrachloromethane (6 ml) was poured into tetrahydrofuran (50 ml) at 0–5°C and this temperature was kept throughout the reaction. The yellow precipitate formed was stirred for 1/2 h, pyridine (2 ml) and 2-furyl 2-thienyl ketone (1.78 g, 0.1 mol) were added and stirring was continued for another 1/2 h. The carbanion prepared from methyl cyanoacetate (1 g, 0.1 mol) and sodium hydride (0.5 g) in tetrahydrofuran (10 ml) was introduced, the mixture stirred for additional 48 h, decomposed with water, washed with a saturated NaCl solution (100 ml), the product extracted with ether and worked up in a usual manner. Yield 1.6 g (60.8%). The crude product was crystallized from ethanol.

Kinetic Measurements

The UV-spectra of the synthesized compounds listed in Table I were recorded with a UV-VIS Zeiss spectrophotometer in 1 cm cells at a $3-5 \cdot 10^{-5} \text{ mol} \cdot \text{l}^{-1}$ concentration in dioxane. The reaction mixture to be measured, consisting of methyl cyanoacetate (7.68 g, $7.6 \cdot 10^{-2} \text{ mol}$), acetic acid (0.4 g, $6 \cdot 10^{-3} \text{ mol}$), ammonium acetate (0.5 g, $6 \cdot 10^{-3} \text{ mol}$) and the respective ketone ($4 \cdot 10^{-5} \text{ mol}$), dissolved in dioxane up to 40 ml was placed into a flask provided with a reflux condenser fitted with a calcium chloride tube and heated in a thermostat set to 80°C. The sample (0.04–0.12 ml) withdrawn in convenient intervals was diluted with dioxane to a $8 \cdot 10^{-5} - 2.4 \cdot 10^{-4} \text{ M}$ concentration and the amount of the product was determined spectrophotometrically. The kinetics of the condensation with acetylfuran was also measured at 25, 40 and 60°C and the activation energy was calculated. The kinetics of the condensation with isopropyl 2-furyl ketone was recorded at 60, 70 and 80°C. To compare the activation energy also the condensation with 2-furaldehyde was measured at 15, 25, 30, 40 and 80°C under the same reaction conditions.

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