STUDIES IN THE FURAN SERIES

XLVIII. Alkylation and Dimerization of 2-Furylacetonitrile*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 5, No. 3, pp. 411–416, 1969

UDC 547.722.2'725:542.951

Alkylation of 2-furylacetonitrile with alkyl halides is a convenient method for the synthesis of mono- and di-α-substituted 2-furylacetic acids. Alkylation is accompanied by hydrolysis of the 2-furylacetonitrile to 2-furylacetic acid, and by dimerization to β-amino-α,γ-di-(2-furyl)-crotononitrile. The latter is also obtained by reaction of 2-furylacetonitrile with phenylmagnesium bromide, phenyl furfuryl ketone being obtained in only insignificant amounts. The ketone is also formed by the reaction of 2-furylacetyl chloride with diphenylcadmium.

The convenient synthesis of 2-furylacetonitrile (I) which we have developed [2] makes possible a number of syntheses based upon it. The present paper reports detailed investigations of the alkylation of this compound, with the aim of synthesizing alkyl-2-furylacetonitriles.

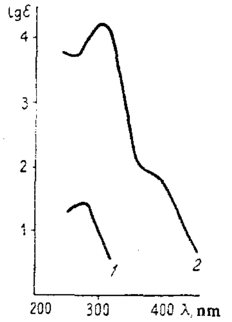
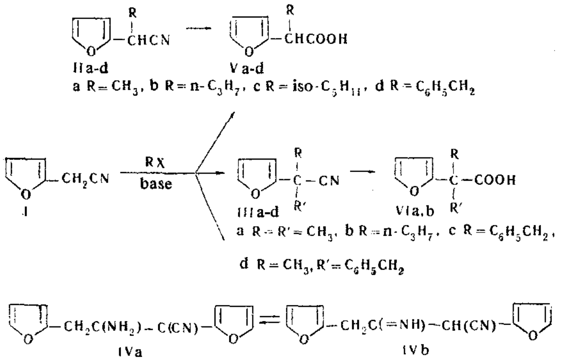
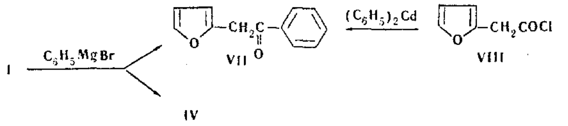


Fig. 1. UV Spectra:
1) 2-furylacetonitrile;
2) dimer IV.

The alkylating agents which we have used are methyl iodide, propyl bromide and iodide, isoamyl bromide, and benzyl chloride (we have previously described the alkylation of I with ethyl iodide [3]) (see Table 1). The condensations were carried out in the presence of sodium methoxide or ethoxide (in toluene and ethanol), potassium hydroxide (in benzene), or sodamide in liquid ammonia.



Either mono-(II) or dialkylated (III) nitriles may be formed preferentially, depending on the proportion of the reagents and the duration of the reaction. The alkylation of I is also complicated by hydrolysis to 2-furylacetic acid and by dimerization. Prolonged heating of the reaction mixture invariably led to the formation of the 'dimer' of 2-furylacetonitrile, which is a tautomeric mixture of β-amino-α, γ-di-(2-furyl)crotononitrile (**IVa**) and β-imino-α, γ-di-(2-furyl)butyronitrile (**IVb**). We have obtained the same dimer (IV) by the reaction between I and phenylmagnesium bromide. The expected phenyl furfuryl ketone (VII) is formed in insignificant amounts under varying conditions of temperature and proportions of reactants (a recently-published paper [4] describes the reaction of I with benzylmagnesium chloride to give benzyl furfuryl ketone in 13% yield). The main course of the reaction is attack by Grignard reagent on the active α-hydrogen atom of I, followed by the reaction of the resulting organomagnesium derivative with the starting nitrile I with the formation of the dimer **IV**.



The structure of the ketone **VII** was confirmed by independent synthesis from 2-furylacetyl chloride (VIII) and diphenylcadmium.

A separate experiment showed that the dimer IV is formed on heating I with sodium methoxide in toluene. The identity of the dimers obtained from I by three different methods (alkylation, reaction with the Grignard reagent, and treatment with sodium methoxide) was proved by thin-layer chromatography. The molecular weight of IV agreed with the theoretical value.

It is known [5] that dimers of the type of IV can exist in two tautomeric forms, the enamine and the ketimine. IR spectral data on IV show the presence of a primary amino-group, a cyano-group, and a double bond. The UV spectra of the dimer IV and the starting material I differ considerably (see figure) the spectrum of IV, as distinct from I, showing a strong absorption band displaced toward the longer wavelengths. This indicates the presence in the molecule of a conjugated system of double bonds. The IR and UV data indicate that IV exists dominantly in the form IVa.

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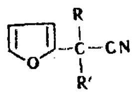
*For part XLVII, see [1]

Table 1



Compd.	R	R′	Meth-od	Time of heating hr.	Bp, °C (press., mm); mp, °C	n_D^{20}	d_4^{20}	MR_D		R_f	Mol formula	Found,		Calculated		Yield
								found	calc.			C	H	C	H	
IIa	CH_3	H	a—d	10	78—79(10)	1.4642	1.0387	32.19	32.73	0.50	C_7H_7NO	69.38	5.89	69.40	5.82	26[a]
IIb	n-C_3H_7	H	a	8	107—107.5(19)	1.4649	0.9830	41.94	41.97	0.60	$C_9H_{11}NO$	72.92	7.70	72.45	7.43	45[a]
IIc	i-C_5H_{11}	H	a	6	65—65.5(2)	1.4625	0.9546	51.09	51.20	0.65	$C_{11}H_{15}NO$	74.83	8.58	74.54	8.53	14
IId	$C_6H_5CH_2$	H	a	8	120—120.5(2) 31—32 (from light petroleum)	1.5434	—	—	—	0.43	$C_{13}H_{11}NO$	79.09	5.77	79.16	5.62	26[b]
IIIa	CH_3	CH_3	a	50	78—78.5(16)	1.4586	0.9949	37.11	37.35	0.62	C_8H_9NO	70.65	6.89	71.09	6.71	60[a]
IIIb	n-C_3H_7	n-C_3H_7	a	40	142—143(46)	1.4625	0.9561	55.05	55.82	0.78	$C_{12}H_{17}NO$	75.34	9.02	75.35	8.96	75
IIIc	$C_6H_5CH_2$	$C_6H_5CH_2$	a	8	60—61 (from a mixture of ether and light petroleum)	—	—	—	—	0.51	$C_{20}H_{17}NO$	83.57	6.07	83.59	5.96	6
IIId[c]	CH_3	$C_6H_5CH_2$	d	—	106—106.5(2)	1.5372	1.0702	61.66	61.46	0.55	$C_{14}H_{13}NO$	79.58	6.28	79.60	6.20	88[c]

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[a] Yield after purification on an alumina column. [b] The dialkylated nitrile **IIIb** was also formed, in 6% yield. [c] Possesses an intense odor of geraniums.

Table 2

2-Furylacetic Acids

Compound	Acid	Time of boiling, hr	Bp, ° C (press., mm); mp, ° C	n_D^{20}	d_4^{20}	MR_D		Mol formula	Found, %		Calculated, %		Yield %
						found	calc		C	H	C	H	
Va	2-(2'-Furyl)propionic	8	79—80(2)	1.4802	1.1610	34.30	34.57	$C_7H_8O_3$	60.17	5.91	59.99	5.75	97
Vb	2-(2'-Furyl)valeric	8	119—120(4)	1.4747	1.0829	43.71	43.81	$C_9H_{12}O_3$	64.18	7.39	64.27	7.19	89
Vc	5-Methyl-2-(2'-furyl)hexanoic	10	125—126(2)	1.4738	1.0379	53.12	53.04	$C_{11}H_{16}O_3$	67.15	8.03	67.32	8.22	65
Vd	3-Phenyl-2-(2'-furyl)propionic	11	47—48*	—	—	—	—	$C_{13}H_{12}O_3$	71.94	5.82	72.26	5.59	75
VIa	2-(2'-Furyl)isobutyric	18	62—62.5**	—	—	—	—	$C_8H_{10}O_3$	62.26	6.43	62.33	6.54	90
VIb	2-n-Propyl-2-(2'-furyl)valeric	20	60—61**	—	—	—	—	$C_{12}H_{18}O_3$	68.23	8.70	68.54	8.63	62

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*From light petroleum and ether.

**From light petroleum.

Table 3

S-Benzylisothiourea salts of 2-furylacetic acids

Acid	Mp of salt °C	Molecular formula	Found, %		Calculated, %	
			C	H	C	H
2-(2'-Furyl)propionic	137—138	$C_{15}H_{18}O_3N_2S$	58.70	6.15	58.80	5.92
2-(2'-Furyl)valeric	138—139	$C_{17}H_{22}O_3N_2S$	61.40	6.75	61.05	6.63
5-Methyl-2-(2'-furyl)hexanoic	125—125.5	$C_{19}H_{26}O_3N_2S$	62.91	7.16	62.96	7.23
3-Phenyl-2-(2'-furyl)propionic	146—147	$C_{21}H_{22}O_3N_2S$	66.03	5.95	65.94	5.80
2-Furylacetic*	150—151	$C_{14}H_{16}O_3N_2S$	57.52	5.69	57.52	5.52
2-(2'-Furyl)butyric [3]	149—150	$C_{16}H_{20}O_3N_2S$	60.18	6.35	59.98	6.29
2-(2'-Furyl)isobutyric	141—141.5	$C_{16}H_{20}O_3N_2S$	59.96	6.33	59.98	6.29
2-n-Propyl-2-(2'-furyl)valeric	142.5—143.5	$C_{20}H_{28}O_3N_2S$	64.00	7.46	63.80	7.50

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*p-Bromophenacyl ester, mp 93-94° C (from aqueous ethanol). Found, %: C 52.09; H 3.59. Calculated for $C_{14}H_{11}O_4Br$, %: C 52.04; H 3.43%.

Alkaline hydrolysis of the monoalkylated nitriles **IIa–d**, and also of the dialkylated nitrile **IIIa**, afforded the corresponding acids **Va–d** and **VIa** in almost quantitative yields (Table 2). Attempted hydrolysis of the dialkylated nitriles **IIIb** and **c** under the usual conditions failed. 2-n-Propyl-2-(2'-furyl)valeric acid (**VIb**) was obtained by prolonged heating of **IIIb** with potassium hydroxide in an autoclave.

EXPERIMENTAL

n-Propyl-2-furylacetonitrile (IIb). a) To a suspension of 6.0 g (0.106 mole) of potassium hydroxide in 50 ml of dry benzene was added a mixture of 10.7 g (0.10 mole) of I and 17.8 (0.104 mole) of propyliodide, and the mixture was boiled with stirring for 8 hr. Water was added to dissolve the precipitate of potassium iodide, the benzene layer separated, and the aqueous layer washed with benzene. The combined benzene extracts were washed with water and dried over magnesium sulfate. Acidification of the aqueous layer, followed by extraction with ether, gave 2.6 g (22%) of 2-furylacetic acid, mp 67–68° C (from light petroleum), in agreement with [6]. Removal of the solvent from the benzene layer gave fractions A and B. Fraction A had bp 90–95° C (8 mm), 9.7 g (65%), n_D^{20} 1.4660. Fraction B had bp 209–214° C (8 mm), 1.1 g. Fraction A was n-propyl-2-furylacetonitrile (**IIb**), shown by thin-layer chromatography on alumina (R_f 0.60) to be contaminated with the starting nitrile (R_f 0.38) and the dialkylated nitrile (R_f 0.78) (in this and all succeeding experiments, grade 2 alumina was used. The best solvent for the separation of the nitriles was a mixture of hexane and ether (2 : 1). All R_f values for nitriles relate to this system. For separation on a chromatographic column, the hexane may be replaced by light petroleum (bp 40–60° C). After chromatographic purification on an alumina column, there was obtained 6.6 g (45%) of **IIb** (constants and analyses are given in Table 1). Fraction B after purification on an alumina column (eluted with chloroform) gave the dimer **IV** as a viscous, bright yellow liquid, bp 175–178° C (2 mm); R_f 0.55 and 0.15 (chloroform) (see below).

Replacement of the propyl iodide by the bromide under the conditions of the foregoing experiment afforded a yield of 17% of nitrile **IIb**, 2-furylacetic acid also being formed in 23% yield.

b) A mixture of 10.7 g (0.10)mole) of I and 17.8 g (0.104 mole) of propyl iodide in 50 ml of dry toluene was boiled for 5 hr with 6.0 g (0.11 mole) of sodium methoxide, and the mixture worked up as above. There was obtained 3.6 g (26%) of **IIb** and 4.6 g (43%) of **IV**, while the aqueous layer yielded 0.8 g (6%) of 2-furylacetic acid.

c) A mixture of 10.7 g (0.10 mole) of **I**, 17.8 g (0.104 mole) of propyl iodide and 2.3 g (0.10 g-at) of sodium dissolved in 50 ml of absolute ethanol was stirred for 2 hr, boiled for 15 hr, the ethanol removed under reduced pressured, and the residue dissolved in the minimum amount of water. The solution was extracted with ether, the extract dried over magnesium sulfate, and the ether removed to give 2.4 g (16%) of **IIb**, 3.1 g (29%) of **IV**, and from the aqueous layer 1.0 g (7%) of 2-furylacetic acid.

d) To a solution of sodamide in liquid ammonia prepared by dissolving 2.4 g (0.105 g-at) of sodium in 300 ml of liquid ammonia in the presence of a trace of ferric nitrate, was added 10.7 g (0.10) mole) of I at -70° C, followed after 2 hr by 18.0 (0.106 mole) of propyl iodide The mixture was stirred for 2 hr at −70° C, 50 ml of dry ether added, and kep overnight. Water was added to dissolve the precipitate, followed by ether extraction to give 5.8 g (39%) of **IIb**.

Replacement of the propyl iodide by the bromide gave, from 10.7 g (0.10 mole) of **I**, and 12.3 g (0.10 mole) of propyl bromide, 3.2 g (21%) of **IIb**.

Di-n-propyl-2-furylacetonitrile (IIIb). A 10.7 g (0.10 mole) quantity of I was boiled for 40 hr as in a) above with a threefold excess of propyl iodide and potassium hydroxide to give 14.3 g (75%) of **IIIb**.

2-(2'-Furyl)valeric acid (Vb). A 1.0 g (6.7 mM) quantity of **IIb** and 15 ml of a 20% solution of potassium hydroxide was boiled for 8 hr until evolution of ammonia ceased. The reaction mixture was extracted with ether to remove unreacted nitrile, and acidified with hydrochloric acid. Re-extraction with ether followed by drying, removal of the ether and distillation afforded 1.0 g (89%) of **Vb** as a colorless liquid which darkened on standing. Acids **Va–d** and **VIa** were obtained similarly (see Table 2).

2-n-Propyl-2-(2'-furyl)valeric acid (VIb). A 3.83 g (0.02 mole) quantity of **IIIb**, 5.6 g (0.1 mole) of potassium hydroxide, 10 ml of water, and 28 ml of methanol were heated in an autoclave for 20 hr at 160° C, the methanol removed by distillation, and the residue worked up in the usual way to give 2.60 g (62%) of **VIb**.

All the acids obtained in this way, and also 2-furylacetic acid and 2-(2'-furyl)butyric acid [3] were characterized as their benzylisothio-urea salts (see Table 3). They were recrystallized from water or aqueous ethanol.

Reaction of I with phenylmagnesium bromide. To a solution of phenylmagnesium bromide from 5.4 g (0.22 g-at) of magnesium and 36.6 g (0.22 mole) of bromobenzene in 180 ml of dry ether was added during 1 hr at 0°C 21.4 g (0.20 mole) of I in 50 ml of dry ether. The mixture was stirred for 1.5 hr at 0° C and 2 hr at room temperature, decomposed with 250 g of ice, acidified with sulfuric acid, extracted with ether and fractionally distilled. The lower-boiling fractions (32–120° C at 7 mm) contained bromobenzene, phenol, diphenyl and the starting nitrile **I**. **Phenyl furfuryl ketone** (**VII**) (1.3 g; 4%) was isolated from the fraction bp 105–125° C (1 mm) as a bright yellow liquid, bp 138–140° C (8 mm); 108–110°C (1 mm); n_D^{20} 1.5680; d_4^{20} 1.1547. Found: C 77.90; 77.87; H 5.71; 5.85 MR_D 52.76. $C_{12}H_{10}O_2$. Calc.: C 77.40; H 5.42; MR_D 52.54. R_f 0.74 (chloroform), 0.49 (benzene). **2,4-Dinitrophenylhydrazone**—orange flakes, mp 187–187.5° C (from aqueous dioxan). Found, %: C 58.48; 58.79; H 3.93; 3.94. $C_{18}H_{14}O_5N_4$. Calc.: C 59.01; H 3.85. **Oxime**—colorless needles, mp 90–90.5° C (from light petroleum), in agreement with [7]. The fraction bp 160–210° C (1 mm) afforded 5.9 g (28%) of **IV**, bp 172–173.5° C (1 mm): R_f 0.55 and 0.15 (chloroform).

Variations in the temperature at which the reaction was carried out (36° C, −20° C), and also the use of a fourfold excess of phenylmagnesium bromide did not result in an improved yield of the ketone **VII**; under all conditions **IV** was formed in yields of 18–30%.

Phenyl furfuryl ketone (VII) from diphenylcadmium and 2-furylacetyl chloride (VIII)*. To a solution of diphenylcadmium [8] (from 0.12 g-atom of magnesium, 0.12 mole of bromobenzene and 0.065 mole of cadmium chloride in 120 ml of dry ether under nitrogen) in dry benzene (120 ml) was added over 10 min at 5° C a solution of 17.4 g (0.12 mole) of **VIII** [2] in 70 ml of benzene. The mixture was stirred for 30 min at 5° C and for 1 hr at 20° C, poured into 100 g of crushed ice, acidified with sulfuric acid and worked up in the usual way to give 4.0 g (20%) of **VII**, bp 154–155° C (13 mm). 2,4-Dinitrophenylhydrazone, mp 187–187.5° C (from aqueous dioxane). A mixed melting point with a sample of the material obtained in the foregoing experiment gave no depression.

Dimerization of I in presence of sodium ethoxide. A 10.7 g (0.10 mole) quantity of **I** in 59 ml of dry toluene was stirred for 2 hr in presence of 6.0 g (0.11 mole) of sodium methoxide and boiled for 3 hr at 110° C. Then water was added, the layers separated, and the aqueous layer washed with toluene. The combined toluene extracts were dried over magnesium sulfate and distilled to yield 4.7 g (46%) of **IV**. Acidification of the aqueous layer gave 1.5 g (12%) of 2-furfurylacetic of mp 67–68° C (from light petroleum). Compound **IV** was a bright yellow, viscous liquid which crystallized on prolonged standing in the refrigerator, mp 37–44° C, bp 175–178° C (2 mm). UV spectrum (chloroform): λ_{max} 303 nm (lgε 4.23) (Fig. 1). IR spectrum chloroform), cm^{-1}: 1632 (double bond), 2198 (C≡N), 3368, 3480 ($-NH_2$). R_f 0.55 and 0.15 (chloroform). Found, %: C 66.98; 67.07; H 4.92, 4.96; N 13.30; 13.11; Mol. wt. 214 (determined by mass-spectrometry on an MI-1305 instrument). Calculated for $C_{13}H_{12}N_2O_2$, %: C 67.28; H 4.71; N 13.08; Mol. wt. 214.23. Hydrolysis of 1.30 g of **IV** by boiling with 20 ml 20% potassium hydroxide solution for 22 hr afforded 0.95 g (60%) of 2-furylacetic acid, mp 67–68° C.

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16 January 1967

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*Attempts to acylate benzene with the acyl chloride **VIII** in presence of aluminum chloride or stannic chloride led to extensive resinification; the presence of **VII** was established by thin-layer chromatography.