PYRROLES FROM KETOXIMES AND ACETYLENE.

30.* THE SYNTHESIS OF 3-ALKYL-2-ARYLPYRROLES

S. E. Korostova, A. I. Mikhaleva,
L. N. Sobenina, S. G. Shevchenko,
and V. V. Shcherbakov

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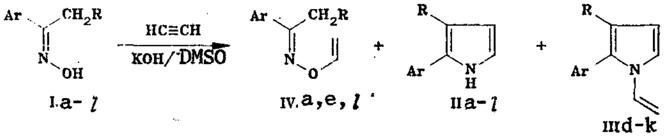
Conditions were found for the synthesis of 3-alkyl-2-arylpyrroles using the Trofimov reaction at 50-70°C both at elevated and atmospheric pressure. O-Vinyloximes and 3H-5-hydroxy-4,5-dihydropyrroles were isolated as intermediates.

3-Alkyl-2-arylpyrroles which were difficult to obtain until recently have been prepared from ketoximes and acetylene by the Trofimov reaction in 38-64% yield [2]. The reaction was carried out in an autoclave at 100°C and 12-14 atm initial acetylene pressure. Milder conditions were sought for this synthesis in order to further simplify the purification of the pyrroles and the preparative isolation of the intermediates, namely, O-vinyloximines [3] and 3H-5-hydroxy--4,5-dihydropyrroles [4]. In accord with the general features of this reaction [5], this required an increase the concentration of alkali and DMSO in the reaction mixture. Thus, the use of an equimolar amount of KOH (relative to the ketoxime) and tenfold excess of DMSO (relative to the total mass of the reagents) permits a substantial reduction in the reaction temperature (to 50-60°C) and the preparation of pure 3-alkyl-2-arylpyrroles and their 1-vinyl derivatives in total yields up to 89%.



Ia, IIa, IVa R=H, Ib, IIb R=Me, Ic, IIc R=Et, Id—IIId R=*n*-Pr, Ie—IVe R=*i*-Pr, I—III f R=*n*-Bu, g R=*n*-Am, h R=*n*-C_6H_{13}, i R=*n*-C_7H_{15}, j R=*n*-C_8H_{17}, k R=*n*-C_9H_{19}, I, II, IVa—k Ar=Ph, *l* R=H, Ar=4-ClC_6H_4

The structure of the starting ketoxime has a significant effect on the composition of the reaction products and the pyrrole yield (Table 1). Thus, 2-phenylpyrrole (IIa) (from acetophenone oxime) is formed at this temperature is about 10% yield. Under the same conditions, pyrrole IIg (from hexyl phenyl ketone oxime) was isolated in 83% yield in addition to the corresponding 1-vinylpyrrole IIIg (6%). In general, upon extending the alkyl chain (R group) from Me to $C_{10}H_{21}$, the total yield of pyrroles II and III initially increases (up to R = C_5-C_6) and then drops while remaining rather high (52-70%). The maximum observed on the curve for the dependence of the product yield on R is apparently only slightly related to the electronic effects of the substituent and is a consequence of the change in the hydrophobic—hydrophilic balance on the starting compounds and final products and their solubility in the reaction mixture. Furthermore, the oximes display a reduced tendency to undergo heterocyclization with increasing electronegativity of R. For example, for acetophenone oxime, the O-vinylation product IVa is formed in 22% yield. Under the conditions studied (50°C, 3 h), IVa is not fully converted to pyrrole IIa. 1-Vinylpyrrole IIIa is completely lacking in the reaction mixture as indicated by gas-liquid chromatography and thin-layer chromatography. It is interesting that a similar result was obtained in the case of methyl p-chlorophenyl ketoxime (I*l*), whose electron-donor properties are less than those for oximes Ia-j due to the presence of the electronegative chlorine atom in the para position of the benzene ring. The yield of pyrrole II*l* under the same conditions is only 8%, while the yield of intermediate O-vinyloxime IV*l* is equal to 17%. In the case of isobutyl phenyl ketoxime (Ie), the reaction does not stop at the vinylation step (the yield of O-vinyloxime IVe

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TABLE 1. Yield of Pyrroles II and III Obtained from Ketoximes* Ia-k

CH₂R	Yield of pyrroles, %		Ketoxime conversion, %
	II	III	
Me	10	traces	—
Et	36	traces	52
Pr-*n*	38	traces	40
Bu-*n*	47	13	90
Bu-*i*	26±2†	4	71
Am-*n*	63	20	100
C_6H_{13}-*n*	83	6	92
C_7H_{15}-*n*	44±3†	8	61
C_8H_{17}-*n*	48	9	89
C_9H_{19}-*n*	49	17	92
$C_{10}H_{21}$-*n*	57	13	92

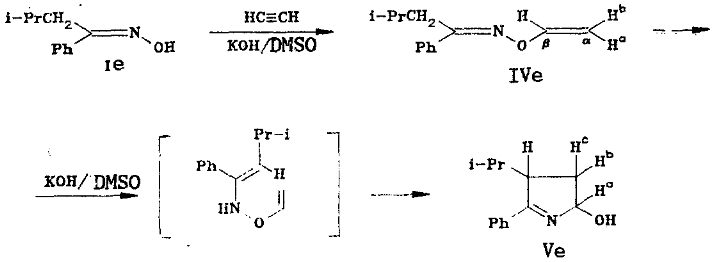
*50-60°C, 3 h 12-14 atom initial acetylene pressure, equimolar amount of KOH relative to the ketoxime and tenfold excess of DMSO relative to the total mass of the reagents.
†From two experiments.

TABLE 2. Conditions and Yield of the Products of the Reaction of Ketoximes with Acetylene at Atmospheric Pressure

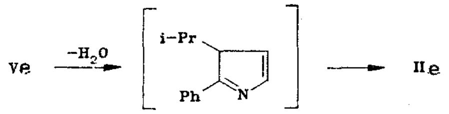
Ketoxime	Reaction temp., °C	Reaction time, h	Yield (GLC), %			Ketoxime conversion, %
			II	III	IV	
Ia*	40	10	traces	not detected	9	15
Ia	60	2,5	traces	not detected	9	22
Ia*	60	10	10	not detected	12	55
Ic	70	5	36	9	not detected	51
Id	50	5	11	0,3	not detected	21
Id	70	5	33	1	not detected	49
Ie	70	5	54	6	not detected	76

*A twofold excess of KOH was used.

is only about 1.5%) and the more stable reaction product is 3-isopropyl-2-phenyl-5-hydroxy-4,5-dihydropyrrole (Ve) obtained in 27 ± 1% yield.*



Dihydropyrrole Ve is converted to pyrrole IIe even upon storage at room temperature and the intermediate β-pyrrolenine could not be detected.



The conversion rate is markedly increased upon heating, especially in the presence of KOH–DMSO. The thermal conversion of dihydropyrrole Ve to pyrrole IIe is clearly seen upon gas–liquid chromatography (GLC) at 170°C column temperature. This conversion is also indicated by IR and PMR spectral methods. The IR spectrum of the mixture obtained upon heating dihydropyrrole Ve in KOH/DMSO shows NH group bands at 3380 and 3440 cm^{-1} while the PMR spectrum shows signals for the 4-H proton as a triplet at 6.17 ppm and 5-H proton as a triplet at 6.77 ppm.

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*From the results of two experiments.

TABLE 3. Physicochemical Constants of Pyrroles

Pyrrole	Bp (mm Hg) [mp], °C	d_4^{20}	n_D^{20}	Found, %			Chemical formula	Calc., %		
				C	H	N		C	H	N
IIe	[67—68]	—	—	84,8	8,2	7,5	$C_{13}H_{15}N$	84,3	8,2	7,6
IIh	155—156 (1—2)	0,9866	1,5669	84,9	9,6	6,6	$C_{16}H_{21}N$	84,5	9,6	6,2
IIi	[46—48]	—	—	84,3	9,6	5,9	$C_{17}H_{23}N$	84,6	9,6	5,8
IIj	168 (1—2)	0,9699	1,5548	84,7	10,0	5,5	$C_{18}H_{25}N$	84,7	9,9	5,5
IIk	[38,5—39,5]	—	—	84,6	10,4	5,0	$C_{19}H_{27}N$	84,7	10,1	5,2

3-Alkyl-2-phenyl-pyrroles IIa, c-e are also readily formed from ketoximes Ia, c-e and acetylene at atmospheric pressure and 50-70°C over 5-10 h with an equimolar amount of KOH,* and tenfold excess of DMSO. Table 2 illustrates the effect of the reaction temperature and duration as well as of the structure of the starting ketoximes on the composition and yield of the final products.

The structures of the compounds synthesized were confirmed by PMR and IR spectroscopy. The compositions were confirmed by elemental analysis and their purity was confirmed by gas-liquid or thin-layer chromatography.

EXPERIMENTAL

The composition of the reaction mixture obtained upon the reaction of ketoximes Ia, c-e with acetylene at atmospheric pressure was determined by gas—liquid chromatography on an LKhM-8MD chromatograph with a katharometer detector using a 1 m × 3 mm column packed with 5% GE-XE-60 silicone on Chromaton N-AW and a 2 litter/h helium gas carrier flow rate. The thermostat temperature was 160-230°C depending on the boiling point of the pyrrole analyzed. The injector temperature was 350°C and the detector temperature was 300°C. The IR spectra were taken on a UR-20 spectrometer neat (IIb-d, f-h, j, IVa, *l*) or in KBr pellets (IIa, e, i, k, *l*, Ve). The PMR spectra were taken on a Tesla BS-487B spectrometer at 80 MHz for CCl_4 solutions with HMDS as the internal standard.

The characteristics of pyrroles IIe, h-j are given in Table 2.

2-Phenylpyrrole (IIa) and O-Vinylacetophenone Oxime (IVa). A. A mixture of 7.5 g (50 mmoles) oxime Ia, 2.8 g (50 mmoles) KOH and 100 ml DMSO was heated with acetylene (12 atm initial pressure) in a rotating steel autoclave at 50°C for 3 h. The reaction mass was diluted with 5 volumes water and extracted with ether. The ethereal extracts were washed with 40% aq. KOH and then water and dried over potassium carbonate. Removal of ether gave 5.2 g of mixture which was subjected to chromatography on an alumina column with 3:1 hexane—ether as the eluent to yield 0.8 g (∿10%) pyrrole IIa, mp 125-127°C and 2 g (22%) O-vinyloxime IVa, bp 83-90°C (3 mm Hg), d_4^{20} 0.9755, n_D^{20} 1.5245. IR spectrum: C=C in the $OCH=CH_2$ group), 3050 (ν_{as} $=CH_2$), 970 (δ_{CH_2}), 985 (ν_{N-O}), 1126, 1150 cm^{-1} (ν_{C-O}). PMR spectrum: 2.13 (3H, s, $CH_3C=N$), 4.03 (1H, d. d, α-H^b, J_{cis} = 6.8), 4.56 (1H, d. d, α-H^a, J_{trans} = 14.2), 6.90 (1H, d. d, β-H, J_{gem} = 1.5 Hz), 7.34-7.36 ppm (5H, m, pH). Found: C, 74.6; H, 6.6; N, 8.5%. Calculated for $C_{10}H_{11}NO$: C, 74.5; H, 6.9; N, 8.7%.

B. A mixture of 13.5 g (100 mmoles) oxime Ia, 5.6 g (100 mmoles) KOH and 190 ml DMSO was added to a reaction flash equipped with a stirrer, reflux condenser and acetylene inlet bubbler. The mixture was heated to 60°C and then acetylene was introduced. The reaction was terminated after 5 h and left standing overnight. Then, an additional 5.6 g (100 mmoles) KOH was added to the reaction mass and acetylene was added for 5 h. Then, 700-800 ml water was added to the cooled reaction mass and the mixture was extracted with ether. The ethereal extracts were washed with water and dried over potassium carbonate. The residue obtained after removal of ether was subjected to chromatography on an alumina column using 3:1 hexane—ether as the eluent to yield 1.4 g (10%) pyrrole IIa, 2 g (12%) O-vinyloxime IVa and 3 g oxime Ia. An additional 3.1 g oxime Ia (55% conversion) was separated from the aqueous layer by acidification 1:1 hydrochloric acid—water and subsequent ether extraction.

3-Hexyl-2-phenylpyrrole (IIh) and 1-Vinyl-3-hexyl-2-phenylpyrrole (IIIh). The reaction of 10.9 g (50 mmoles) oxime Ih and acytelene (12 atm initial pressure) at 50°C for 3 h and standard work-up (see procedure B) gave 1.07 g of a mixture upon which chromatography on an

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*A twofold excess of KOH was used in the synthesis of pyrrole IIa (see Table 2).

alumina column using 3:1 hexane—ether as eluent gave 4.7 g (41%) pyrrole IIh [bp 155-156°C (1-2 mm Hg), d_4^{20} 0.9866, n_D^{20} 1.5669. IR spectrum: 3380, 3420 cm^{-1} (NH). PMR spectrum: 5.94 (1H, t, 4-H), 6.43 (1H, t, 5-H), 7.60 (1H, s, N), 7.16 (5H, s, Ph), 0.8 (3H, t, CH_3), 1.2 [8H, m, $CH_2(CH_2)_4CH_3$], 2.41 ppm (2H, t, $CH_2(CH_2)_4CH_3$), 1.1 g (8%) vinylpyrrole IIIh (PMR and IR spectral data) and 4.3 g oxime Ih (61% conversion).

Pyrroles IIIb-d, f-k were synthesized according to analogous procedures.

3-Isoprpyl-2-phenylpyrrole (IIe) and 3-Isopropyl-2-phenyl-6-hydroxy-4,5-dihydropyrrole (Ve). The reaction of 8.8 g (50 mmoles) oxime Ie, 2.8 g (50 mmoles) KOH in 115 ml DMSO (12 atm initial acetylene pressure) at 50°C for 3 h and work-up according to procedure B gave 8.9 g of a mixture consisting of liquid and crystalline compounds. The crystals were separated from the liquid by filtration on a Schott filter to yield 2.6 g (26%) Ve, mp 133-134°C. IR spectrum: 1108, 3176, 3400 (OH), 1620 (C=N), 1578 (Ph), 1327, 1449, 2870, 2958 cm^{-1} (CH_3, CH). Found: C, 76.5; H, 8.5; N, 7.0%. Calculated for $C_{10}H_{17}NO$: C, 76.8; H, 8.4; N, 6.9%.

The liquid was subjected to chromatography on an alumina column with 3:1 hexane—ether as the eluent to give 2.6 g (28%) pyrrole IIe. IR spectrum: 3380 cm^{-1} (NH). PMR spectrum: 6.17 (1H, t, 4-H), 6.77 (1H, t, 5-H), 3.06 (1H, m, CH), 1.15 (6H, d, $2CH_3$), 7.35 ppm (6H, m, NH, arom. protons). A sample of 2.6 g oxime Ie was returned (71% conversion) and 0.06 of a mixture was obtained consisting of O-vinyloxime IVe and vinylpyrrole IIIe in 1:3 ratio as indicated by PMR spectroscopy.

3-Propyl-2-phenylpyrrole (IId) and 1-Vinyl-3-propyl-2-phenylpyrrole (IIId). A mixture of 3 g (16.9 mmoles) oxime Id, 0.9 g (16.9 mmoles) KOH and 40 ml DMSO was placed into the reaction vessel described in procedure B and heated to 70°C and then acetylene was bubbled into the mixture for 5 h at this temperature. Work-up according to procedure B gave 3.6 g of a mixture consisting of 33% pyrrole IId, 1% vinylpyrrole IIId and oxime Id (49% conversion).

Pyrroles IIc-e were synthesized by analogous procedures. The conditions are indicated in Table 2.

2-(p-Chlorophenylpyrrole (II*l*) and O-Vinyl-p-chloroacetophenone Oxime (IV*l*). A mixture consisting of 17 g (100 mmoles) oxime I*l*, 5.6 g (100 mmoles) KOH and 225 ml DMSO was heated at 50°C for 3 h in the presence of acetylene (14 atm initial pressure). Work-up according to procedure B gave 1.4 g (8%) pyrrole II*l*, mp 140°C [6], 3.3 g (17%). O-vinyloxime IV*l*, d_4^{20} 1.1026, n_D^{20} 1.5620. IR spectrum: 1624 ($\nu_{C=C}$ in the $OCH=CH_2$ group), 3080 (ν_{as} $=CH_2$), 967 (δ_{CH_2}), 1140, 1168 cm^{-1} (ν_{C-O}). PMR spectrum: 2.13 (3H, s, CH_3C-N), 4.05 (1H, d. d, α-H^b, J_{cis} = 6.8), 5.54 (1H, d. d, α-H^a, J_{trans} = 14.2), 6.88 (1H, d. d, β-H, J_{gem} = 1.6 Hz), 7.32 ppm (4H, m, NH, arom. protons). Found, C, 62.6; H, 5.6; N, 6.8; Cl, 17.3%. Calculated for $C_{10}H_{10}ClNO$: C, 62.4; H, 5.2; N, 7.2; Cl, 18.1%.

Thermolysis of 3-Isopropyl-2-phenyl-5-hydroxy-4,5-dihydropyrrole (Ve) to Give Pyrrole IIe. A mixture of 0.1 g Ve, 0.4 g KOH and 1.5 ml DMSO was heated for 3 h at 95-97°C in a flask equipped with a reflux condenser, diluted with water and extracted with ether. The removal of ether gave 0.08 g of a compound corresponding in its PMR and IR spectra to pyrrole IIe.

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