PYRROLES FROM KETOXIMES AND ACETYLENE
42.* FEATURES OF THE SYNTHESIS OF NEW 2-ARYLPYRROLES

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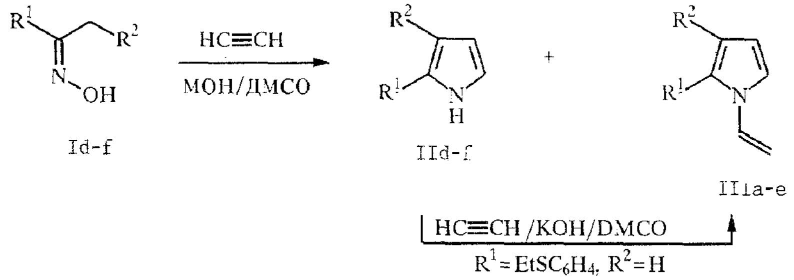
The respective 2-aryl- and N-vinyl-2-arylpyrroles were obtained by the reaction of the oximes of alkyl aryl ketones with acetylene in the superbasic medium MOH (M = Li, K)—DMSO. Their yields depended largely on the structure of the ketoximes and on the reaction conditions.

The Trofimov reaction and its various forms are being used more and more frequently for the production of substituted pyrroles and their N-vinyl derivatives [2-6]. We investigated the condensation of a series of new alkyl aryl ketoximes (Ia-f) with acetylene.



I—IIIa R^1=4-PhC_6H_4, R^2=H; I—III b R^1=4-MeOC_6H_4, R^2=Pr-*i*; I—III c R^1=4-ClC_6H_4, R^2=Pr-*i*; I—IIId R^1=PhCH_2, R^2=Ph; I—IIIe R^1=4-EtSC_6H_4, R^2=H; I, IIf R^1=4-PhSC_6H_4, R^2=H; M=Li, K

Some of the typical experiments are given in Table 1 to illustrate the obtained results. It follows from the data in Table 1 that the final result of the reaction depends largely on the structure of the ketoxime and on the reaction conditions. Thus, N-vinyl-2-(4-phenylphenyl)pyrrole (IIIa) was mainly formed with a yield of 68% from 4-phenylacetophenone oxime (Ia) with acetylene under pressure in the presence of potassium hydroxide at 100°C, while the pyrrole (IIa) was obtained with a yield of 16% under these conditions (expt. 2). With lithium hydroxide, which usually catalyzes the construction of the pyrrole ring sufficiently actively in the reaction of alkyl aryl ketoximes with acetylene and is almost inactive in the vinylation of the intermediately formed pyrroles [8,9], it is possible to synthesize the pyrrole (IIa) free from its N-vinyl derivative with a higher yield (42%, expt. 1). On account of the reduced catalytic activity of lithium hydroxide compared with potassium hydroxide [9] the vinylation rate of the ketoxime (Ia) and the rearrangement rate of the intermediate (O-vinyl-4-phenylacetophenone oxime) to the pyrrole (IIa) are reduced, and the conversion of the ketoxime (Ia) in the same time is consequently reduced from 100 to 67%. In addition, the reaction is accompanied by regeneration of the 4-phenylacetophenone (yield 10%).

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*For Communication 41, see [1].

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TABLE 1. The Dependence of the Yield of the Pyrroles and N-Vinylpyrroles on the Structure of the Ketoximes and on the Reaction Conditions

Expt.	Ketoxime	Ketoxime—MOH ratio, mole	M	Initial acetylene pressure, kPa	Temperature, °C	Time, h	Yield, %	
							II	III
1	I a	1 : 1	Li	980,66	100	3	41,5	Traces
2	I a	1 : 1	K	1176,80	100	3	15,5	67,7
3	I b	1 : 1	K	1176,80	100	3	Traces	75,0
4	I b	1 : 1	K	1176,80	90	3	26,4	48,0
5	I c	1 : 1,2	K	1372,93	100	3	Traces	76,0
6	I c	1 : 1,2	K	1372,93	90	3	41,0	49,1
7	I d	1 : 2	Li	980,66	110	3	34,3	~7,0
8	I e	1 : 1	K		96	5	47,4	~1,0
9	I f	1 : 1	K		96	5	48,4	~1,0

Note: An excess of acetylene was used in all the experiments, an 8-10-fold excess of DMSO (on the total weight of the ketoxime and MOH) was used in expts. 1-8, and a 20-fold excess of DMSO was used in expts. 8-9, conducted at atmospheric pressure.

Like other oximes of the alkyl aryl ketone series [8], isobutyl 4-methoxyphenyl (Ib) and isobutyl 4-chlorophenyl (Ic) ketoximes react readily with acetylene under pressure at 100°C, giving high yields (75 and 76%, expts. 3 and 5 respectively) of N-vinylpyrroles (IIIb, c). If the reaction temperature is reduced by 10°C in the same catalytic system KOH—DMSO, the vinylation rate of the ketoximes (Ib, c), the heterocyclization rate of the O-vinyloximes to the pyrroles (IIb, c), and the vinylation rate of the latter are reduced, and the N-vinylpyrroles (IIIb, c) are formed with yields of only 48 and 49% (expts. 4 and 6). The reaction mass contains the pyrroles (IIb, c) that did not succeed in entering into reaction with the acetylene. The overall yield of the pyrroles (IIb, IIIb) here remains high (74%, expt. 4). The overall yield of the pyrroles (IIc, IIIc) is 90% (expt. 6), i.e., is 14% higher than the yield of N-vinylpyrrole (IIIc) in expt. 5. This is explained by the increased thermal polymerization of the intermediate and final reaction products at 100°C [8].

The ease of formation of the N-vinylpyrroles (IIIb, c) is due to the increased basicity of the initial ketoximes and intermediately formed pyrroles compared with acetophenone oxime and 2-phenylpyrrole, for example, on account of the presence of the alkyl radicals in their molecules [8] [i-C_4H_9 in the ketoximes (Ib, c) and i-C_3H_7 in the pyrroles (IIb, c)]. It would appear that the ketoxime (Ia), containing an electron-withdrawing group (C_6H_5—C_6H_4), would enter into reaction with acetylene with significantly greater difficulty than the ketoximes (Ib, c) under analogous conditions, giving the N-vinylpyrrole (IIIa) with a small yield. However, its yield was fairly high (68%, expt. 1), and this was secured by the enhanced nucleophilicity of the 2-(4-phenylphenyl)pyrrolyl anion (on account of the reduction in the ionization potential [10]) and, consequently, the increased vinylation rate of the pyrrole (IIa). It was noticed that in condensation with acetylene in the presence of potassium hydroxide in DMSO the dibenzyl ketoxime (Id) forms N-vinyl-2-benzyl-3-phenylpyrrole (IIId) with a yield of 48%.

However, the possible synthesis of the unvinylated pyrrole (IId) has not so far been achieved. In the hope of obtaining it with a good yield we conducted the condensation of the ketoxime (Id) with acetylene, using the catalytic pair LiOH—DMSO and simultaneously increasing the LiOH content and increasing the temperature by 10°C compared with [11]. As a result of intensified deoximation (dibenzyl ketone was detected by GLC), resinification, and the formation of unidentified side products (TLC) and also the vinylation of the pyrrole (IId) the yield of the latter amounted to only 34%. In this case N-vinylpyrrole (IId) was formed (~7%), and this indicated loss of selectivity by the LiOH—DMSO system in the reaction of acetylene with the ketoxime (Id). This probably results the enhanced basicity of the ketoxime (Id) (the presence of the two $C_6H_5CH_2$ groups). We obtained the recently unknown 2-(4-ethylthio)- and 2-(4-phenylthio)pyrroles (IIe, f), which were first synthesized by the "vinyl chloride" version of the Trofimov reaction [6], by reaction of the ketoximes (Ie, f) with acetylene at atmospheric pressure and 96°C and obtained yields of 47 and 48% respectively (expts. 8, 9).

TABLE 2. The IR and PMR Spectra of the Pyrroles (IIa-f)

Pyrrole	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
II a	3415 (NH); 1490, 1600 (C=C of pyrrole and benzene ring) 3010 3045 (C—H$_{arom}$)	9,30 (1H, b, NH); 7,61, 7,37 (5H, m, C_6H_5, 4H, m, C_6H_4); 8,80 (1H, m., 5-H); 6,50 (1H, m., 4-H); 6,16 (1H, m., 3-H)
II b	3340 (NH); 1520, 1613 (C=C of pyrrole and benzene ring); 3000 (C—H$_{aro}$); 2850 (OCH_3); 2900, 2940 (H—C_{sp3})	7,91 (1H, b, NH); 7,32, 6,92 (4H, m., C_6H_4); 6,75 (1H, t, 5-H); 6,22 (1H, t, 4-H); 3,82 (3H, s, CH_3O); 3,06 (1H, m, >CH—); 1,21 [6H, d, $(CH_3)_2$]
II c	3410 (NH); 1495, 1600 (C=C of pyrrole and benzene ring); 2853 2930, 2962 (H—C_{sp3})	7,95 (1H, b., NH); 7,32 (4H, m., C_6H_4); 6,23 (1H, t, 5-H); 6,79 (1H, t, 4-H); 3,06 (1H, m, >CH—); 1,20 [6H, d., $(CH_3)_2$]
II d	3345 (NH); 1490, 1590 (C=C of pyrrole and benzene ring); 3050 (C—H$_{arom}$)	7,70 (1H, b, NH); 7,10...7,60 [10H, m., $(C_6H_5)_2$]; 6,61 (1H, t, 4-H); 4,10 (2H, m, CH_2)
II e	3385, 3430 (NH), 1500, 1600 (C=C pyrrole and benzene ring); 530 650 (C—S); 2870, 2970 (H-C_{sp3})	8,21 (1H, b, NH); 6,82 (1H, m, 5-H); 6,48 (1H, m, 4-H); 6,27 (1H, m, 3-H); 7,32 (4H, m, C_6H_4); 2,92 (2H, q., CH_2); 1,28 (3H, t, CH_3)
II f	3390, 3435 (NH); 1498, 1590 (C=C of pyrrole and benzene ring); 540 (C—S)	8,23 (1H, b. NH); 6,85 (1H, m, 5-H); 6,49 (1H, m, 4-H), 6,22 (1H, m, 3-H); 7,42 (9H, m, C_6H_5, C_6H_4)

If vinyl chloride is replaced by acetylene, the synthesis of the pyrroles (IIe, f) can be realized under milder temperature conditions (96°C instead of 130°C), while preserving the previous yield [pyrrole (IIe)] or increasing it by 2.5 times [pyrrole (IIf)]. The vinyl derivatives of these pyrroles are hardly formed at all under the investigated conditions (yield ~1%). For example, the moderate yields of the pyrroles (IIe, f) compared with 2-phenyl-3-butylpyrrole (63%) and 2-phenyl-3-amylpyrrole (83%), obtained earlier under even milder conditions (50-60°C) [12], are probably due to possible cleavage of the C–S bond [13], leading to the formation of undesirable sulfur-containing compounds. The N-vinyl derivatives of the pyrroles (IIe, f) can be obtained by direct vinylation at atmospheric pressure. During the vinylation of the pyrrole (IIe) a mixture consisting of N-vinyl-2-(4-ethylphenyl)pyrrole (IIIe), the initial pyrrole, and an unidentified compound in ratios of 8:16:1 (GLC) was formed. The vinylpyrrole (IIIe) was isolated from this mixture with a yield of 48%, which is almost seven times greater than the yield of the same vinylpyrrole obtained from the ketoxime (Ie) and vinyl chloride [6].

The structure of the synthesized pyrroles (IIa-f) and N-vinylpyrroles (IIIa-e) was determined from the IR and PMR spectra (Tables 2 and 3).

EXPERIMENTAL

The composition of the reaction mixture and the purity of the obtained compounds were determined by GLC on a Tsvet 100 chromatograph (flame-ionization detector, 0.8 m × 3 mm column, 5% of silicone XE-60 on Chromaton N-AW, helium, thermostat temperature 160-210°C, evaporator temperature 250-300°C). The IR spectra were recorded on a Specord 75 IR or UR-20 instrument in microlayers or in tablets with potassium bromide. The PMR spectra were obtained on a Tesla BS-487B spectrometer at 100 MHz.

2-(4-Phenylphenyl)pyrrole (IIa) ($C_{16}H_{13}N$). In a 1-liter steel rotating autoclave we placed 21.1 g (0.1 mole) of the ketoxime (Ia), 2.4 g (0.1 mole) of lithium hydroxide, and 200 ml of DMSO. Acetylene (980.66)* was delivered from a bottle. The autoclave was heated to 100°C and was kept at this temperature while still rotating. It was then cooled to room temperature. The reaction mixture was diluted with 60 ml of water, the precipitate was filtered off, and 18.9 g of a mixture was obtained. By column chromatography on aluminum oxide (3:1 hexane—acetone) we isolated 9.1 g (42%) of the pyrrole (IIa) (mp 213-214.5°C), 2 g (10%) of 4-phenylacetophenone, and 6.9 g of the ketoxime (Ia).

N-Vinyl-2-(4-phenylphenyl)pyrrole (IIIa) ($C_{18}H_{15}N$). Similarly, from 21.1 g (0.1 mole) of the ketoxime (Ia), 5.6 g (0.1 mole) of potassium hydroxide in 200 ml of DMSO, and acetylene (1176.80) at 100°C we obtained 22.8 g of a precipitate containing vinylpyrrole (IIIa) and pyrrole (IIa). By chromatography on a column of aluminum oxide (3:1 hexane—ether) we isolated 16.6 g (68%) of the vinylpyrrole (IIIa) (mp 120-122°C) and 3.4 g (16%)of the pyrrole (IIa).

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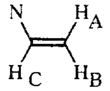
*Here and subsequently the initial pressure (kPa) is given in parentheses.

TABLE 3. The NMR Spectra of the N-Vinylpyrroles (IIIa-e)

Vinyl-pyrrole ring	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm
III a	1620 (C=C, NCH=CH$_2$);.1470. 1585 (C=C of pyrrole and benzene rings) 3030, 3115 (C—H$_{arom}$	5,05 (1H,q., A—H); 4,60 (1H, q, B—H); 6,85 (1H, s C—H); 6,26 (2H,m , 3-H, 4-H); 7,11 (1H,q , 5-H); 7,2...7,5 (9H, m , C_6H_5, C_6H_4)
III b	1615 (C=C, NCH=CH$_2$); 1499, 1596 C=C of pyrrole and benzene rings 3010, 3030, 3109 (C—H $_{arom}$)	4,93 (1H,q , A—H); 4,47 (1H, q, B—H); 6,61 (1H, s, C—H); 6,17 (1Hd ., 4-H); 7,0 (1H,q ., 5-H); 2,74 (1H, m, >CH—); 1,12 [3H, d (CH$_3$)$_2$]; 6,80, 7,30 (4H, m, C_6H_4); 3,94 (3H, s, CH_3O)
III c	1630 (C=C, NCH=CH$_2$); 1485 C=C of pyrrole and benzene rings 3030, 3060, 3080 (C—$_{arom.}$); 2845, 2905, 2940 (H—C$_{sp3}$)	5,0 (1H, q, A—H); 4,51 (1H,q ., B—H); 6,55 (1H, q, C—H); 6,22 (1H, d, 4-H); 7,03 (1H, d, 5-H); 2,73 (1H,m , CH—); 1,11 [6H,d ., (CH$_3$)$_2$]; 7,95, 7,21 (4H,m , C_6H_4)
III d	1642 (C=C, NCH=CH$_2$); 1498, 1600 C=C of pyrrole and benzene rings 3025, 3065, 3090 (C—H$_{arom}$); 2920 (H—C$_{sp3}$)	5,07 (1H, q, A—H); 4,55 (1H, q, B—H); 6,68 (1H, s , C—H); 6,43 (1H,d , 4-H); 7,07 (1H, d 5-H); 7,0, 7,5 (10H,m , 2C_6H_5); 4,16 (2H, s CH_2)
III e	1620 (C=C, NCH=CH$_2$); 1480, 1585 C=C of pyrrole and benzene rings 3040 (C—H$_{arom}$);570(C—S); 2845, 2950 (H—C$_{sp3}$)	5,13 (1H,q , A—H); 4,67 (1H,q , B—H); 6,86 (1H, s, C—H); 6,24 (2H, m, 3-H, 4-H); 7,08 (1H, q, 5-H); 7,29 (4H,s , C_6H_4); 2,94 (2H, q, CH_2); 1,34 (3H, t, CH_3)



, $^2J_{AB}$ =0,8 ; $^3J_{AC}$ =15 ; $^3J_{BC}$ =9 Hz.

2-(4-Methoxyphenyl)-3-isopropylpyrrole (IIb) ($C_{14}H_{15}NO$) and N-Vinyl-2-(4-methoxyphenyl)-3-isopropylpyrrole (IIIb) ($C_{16}H_{19}NO$). A. From 6.2 g (29 mmole) of the ketoxime (Ib) and acetylene (1176.80) in the presence of 1.6 g (29 mmole) of potassium hydroxide and 80 ml of DMSO at 90°C 3 h after dilution of the reaction mass with water (300 ml), extraction with ether (5 × 50 ml), drying with potassium carbonate, and vacuum distillation we obtained a mixture, from which by column chromatography with aluminum oxide (3:1 hexane—ether) we isolated 1.7 g (26%) of the pyrrole (IIb) (mp 61-63°C) and 3.47 g (48%) of the vinylpyrrole (IIIb); bp 140-142°C (2.6-3.9 hPa), d_4^{20} 1.0274, n_D^{20} 1.5792.

B. From 15 g (0.72 mmole) of the ketoxime (Ib) and acetylene (1176.80) in the presence of 4.5 g (80 mmole) of potassium hydroxide and 180 ml of DMSO at 100°C 3 h after the treatment described above by fractional distillation under vacuum we obtained 13.1 g (75%) of the vinylpyrrole (IIIb).

2-(4-Chlorophenyl)-3-isopropylpyrrole (IIc) ($C_{13}H_{14}ClN$) and N-Vinyl-2-(4-chlorophenyl)-3-isopropylpyrrole (IIIc) ($C_{15}H_{16}ClN$). A. From 5.3 g (25 mmole) of the ketoxime (Ic) and acetylene (1372.93) in the presence of 1.4 g (25 mmole) of potassium hydroxide and 70 ml of DMSO at 90°C after the treatment described for the pyrrole (IIb) we obtained 2.26 g (41%) of the pyrrole (IIc) (mp 49-52°C) and 3.02 g (49%) of the vinylpyrrole (IIIc); bp 125-126°C (2.6 hPa), d_4^{20} 1.0759, n_D^{20} 1.5846.

B. From 7.7 g (36 mmole) of the ketoxime (Ic) and acetylene (1372.93) in the presence of 2.4 g (43 mmole) of potassium hydroxide and 100 ml of DMSO at 100°C by the method described for the vinylpyrrole (IIIb) we obtained after 3 h 6.8 g (76%) of the vinylpyrrole (IIIc).

2-Benzyl-3-phenylpyrrole (IId) ($C_{17}H_{15}N$) and N-Vinyl-2-benzyl-3-phenylpyrrole (IIId) ($C_{19}H_{17}N$). From 22.5 g (0.1 mole) of the ketoxime (Id) and acetylene (980.66) in the presence of 4.8 g (0.2 mole) of lithium hydroxide and 200 ml of DMSO at 110°C by the method described for the pyrrole (IIa) we obtained after 3 h 15.5 g of a mixture, from which by column chromatography with aluminum oxide (3:1 hexane—ether) we isolated 8 g (34%) of the pyrrole (IId) (mp 82-84°C) and 1.81 g (7%) of the vinylpyrrole (IIId); mp 50-52°C. Published data [11]: mp 50-51°C.

2-(4-Ethylthiophenyl)pyrrole (IIe) ($C_{12}H_{13}NS$). A mixture of 0.7 g (12.5 mmole) of potassium hydroxide and 75 ml of DMSO, heated to 96°C, was saturated with acetylene for 10 min (atmospheric pressure), 2.43 g (12.4 mmole) of the ketoxime (Ie) was added, and acetylene was bubbled with vigorous stirring for 5 h. The cooled mass was poured into 300 ml of cold water and extracted with ether. The extracts were washed with water and dried with potassium carbonate. The residue obtained after removal of the solvent was fractionated on a column of aluminum oxide (3:2 hexane—ether), and 2 g of the pyrrole (IIe) containing unidentified impurities was obtained. During repeated fractionation on plates with a thin unfixed layer of aluminum oxide we eluted with ether 1.2 g (47%) of the pyrrole (IIe) in the form of grey plates with a pearly luster; mp 129-130°C. Here we also isolated 0.01 g of an unidentified compound in the form of greenish-grey plates; mp 180-181°C.

2-(4-Phenylthiophenyl)pyrrole (IIf) ($C_{16}H_{13}NS$). Acetylene was bubbled with vigorous stirring (atmospheric pressure) for 5 h into a mixture of 3 g (12.3 mmole) of the ketoxime (If), 0.7 g (12.5 mmole) of potassium hydroxide, and 75 ml of DMSO, heated to 96°C. The reaction mass was cooled and poured into 300 ml of cold water. The precipitate was separated, and 2.5 g of a grey substance was obtained. A further 0.5 g was extracted from the aqueous layer with ether. From the total mass (3 g) of the crude substance, dissolved in ethanol, by chromatography on plates with aluminum oxide (thin unfixed layer, 50:1 ether—ethanol) we extracted 1.5 g (48%) of the pyrrole (IIf); mp 180°C (carbonizes).

N-Vinyl-2-(4-ethylthiophenyl)pyrrole (IIIe) ($C_{14}H_{15}NS$). From 0.5 g (2 mmole) of the pyrrole (IIe) and acetylene at atmospheric pressure in the presence of 0.7 g (12.5 mmole) of potassium hydroxide and 30 ml of DMSO at 120°C we obtained after 5 h 0.5 g of a mixture, from which by chromatography on plates with a thin unfixed layer of aluminum oxide with a 3:1 mixture of ether and hexane as eluant we isolated 0.27 g (48%) of the vinylpyrrole (IIIe); bp 160-162°C (3.25 hPa), d_4^{20} 1.0685, n_D^{20} 1.6338.

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