PYRROLES FROM KETOXIMES AND ACETYLENE

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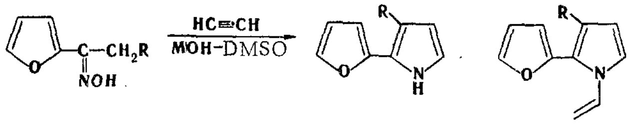
2-(2-Furyl)pyrroles and 1-vinyl-2-(2-furyl)pyrroles were obtained in up to 80% yields in the reaction of ketoximes of the furan series with acetylene in MOH—dimethyl sulfoxide (M = Li, K) superbase media.

A systematic study of the reaction of ketoximes with acetylene in the alkali metal hydroxide—dimethyl sulfoxide (DMSO) superbase system, which leads to pyrroles and their 1-vinyl derivatives, showed that ketoximes that have at least one methyl or methylene group adjacent to the oxime function can undergo this reaction. The previously unknown 1-vinyl-2-substituted and 2,3-disubstituted pyrroles were synthesized by this method [1].

Information regarding the participation of oximes of the furan series in this reaction is limited to our preliminary communications regarding the preparation of 1-vinyl-2-(2-furyl)-3-alkylpyrroles [2] and the peculiarities of the spin—spin coupling in their PMR spectra [3]. The one-step synthesis of 2-(2-furyl)pyrrole by cyclization of N-allyl-α-chloroimines [4] has also been described, while 2-furylpyrroles and particularly their 1-vinyl derivatives are promising reagents for fine organic synthesis, as well as starting compounds for the preparation of biologically active substances, including medicinal preparations. It is felt [5] that 2-hetarylpyrroles are of great interest for chemotherapy.

The experimental conditions for carrying out the reaction of alkyl furyl ketoximes with acetylene are described in detail for the first time in the present paper.



Ia-f IIa, b IIIa-f

M=Li, K; I, II, III a R=H; b R=CH_3; c R=C_2H_5; d R=n-C_3H_7; e R=i-C_3H_7; f R=n-C_4H_9

Under conditions similar to those previously found (100°C, ketoxime—KOH molar ratio 5:3, excess acetylene under an initial pressure of 14-16 atm [1]), methyl furyl ketoxime (Ia) reacts with acetylene to give amixture of vinylpyrrole IIIa and its nonvinylated precursor IIa in a ratio of 4:1 (PMR) in 71% yield (55 and 16%, respectively). Under similar conditions 1-vinylpyrrole IIIb is formed in 8% yield, and the corresponding NH-pyrrole is formed in 8% yield from ethyl furyl ketoxime (Ib). Only 1-vinylpyrrole IIIb can be obtained in 65% yield at a higher temperature (130°C) and an equimolar ratio of Ib to KOH. It should be noted that lithium hydroxide, which selectively catalyzes the step involving the synthesis of the pyrrole ring, does not have a selective effect in the analogous reaction with methyl phenyl and phenyl benzyl ketoximes [6]: A mixture of furylpyrrole IIa and its vinyl derivative IIIa in a ratio of 3:2 is formed from ketoxime Ia and acetylene even at 100°C, and the overall yield of pyrroles in this case is considerably lower than with KOH (35% instead of 72%). The following conditions are better for the synthesis of 1-vinylpyrroles IIIa-f: a reaction temperature of 110-130°C, excess acetylene, a reaction time of 3 h, and a ketoxime to KOH ratio of 1:1. The yields of pyrroles IIIa-f under these conditions range from 50 to 85% (Table 1). The reaction rate is too low at temperatures below 100°C, while at temperatures above 130°C side reactions with the participation of both the

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TABLE 1. Yields and Physical Constants of Pyrroles IIa, b and IIIa-f*

Compound	bp, °C (mm) or mp, °C	d_4^{20}	n_D^{20}	Yield, %
IIa	41	—	—	22
IIb	101 (3)	0,9674	1,5785	23
IIIa	75—76 (3)	1,0886	1,5977	50
IIIb	88 (3)	1,0803	1,5775	85
IIIc	96 (1)	1,0492	1,5649	65
IIId	112—114 (3)	1,0834	1,5592	57
IIIe	118 (1)	0,9954	1,5545	81
IIIf	115 (5)	1,0030	1,5557	64

*Satisfactory microanalytical data (C, H, and N) were obtained for all of the compounds.

TABLE 2. UV and IR Spectra of the Synthesized IIa and IIIa-f*

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, cm^{-1}
IIa	198 (4,04), 279 (4,25)	595, 725, 795, 887, 942, 1010, 1030, 1080, 1108, 1158, 1212, 1282, 1500, 1620, 2930, 3120, 3430
IIIa	—	595, 717, 795, 877, 902, 965, 996, 1020, 1070, 1085, 1155, 1180, 1220, 1252, 1293, 1320, 1355, 1375, 1424, 1447, 1472, 1500, 1537, 1612, 1642, 2930, 3120, 3140
IIIb	204 (4,10), 267 (4,22)	595, 650, 730, 807, 862, 895, 965, 1007, 1027, 1077, 1150, 1202, 1230, 1305, 1372, 1387, 1417, 1485, 1507, 1567, 1646, 2870, 2930, 3120, 3140
IIIc	204 (4,08), 270 (4,17)	597, 665, 732, 810, 862, 897, 944, 965, 993, 1080, 1155, 1205, 1231, 1270, 1315, 1370, 1382, 1415, 1460, 1480, 1505, 1550, 1612, 1642, 2880, 2940, 2970, 3120, 3140
IIId	198 (4,20), 264 (4,22)	602, 655, 730, 805, 860, 895, 962, 990, 1020, 1080, 1155, 1212, 1230, 1312, 1380, 1415, 1480, 1504, 1550, 1612, 1642, 2880, 2940, 2970, 3120, 3140
IIIe	200 (4,20), 265 (4,13)	595, 665, 700, 738, 807, 865, 897, 970, 985, 1000, 1025, 1060, 1080, 1160, 1205, 1240, 1315, 1370, 1385, 1415, 1470, 1480, 1510, 1550, 1612, 1642, 2880, 2930, 2965, 3120, 3140
IIIf	—	597, 650, 695, 730, 815, 870, 897, 970, 997, 1026, 1080, 1160, 1215, 1240, 1315, 1385, 1420, 1480, 1510, 1550, 1612, 1642, 2860, 2870, 2930, 2965, 3120, 3140

*The PMR spectra of pyrroles IIb and IIIb, c, e, f are presented in [4].

starting compounds (deoximation of ketones, as evidenced by the absorption band at 1680 cm^{-1} in the IR spectra of the reaction mixture), as well as the desired products (thermopolymerization with respect to the vinyl group, which gives rise to a decrease in the yields of the vinylpyrroles), become appreciable. At 130-140°C alkyl furyl ketoximes readily form 1-vinylpyrroles also at atmospheric pressure, although the reaction time increases to 6-8 h. A mixture of pyrrole IIb (18.5%) and vinylpyrrole IIIb (33%) is obtained from ketoxime Ib and acetylene after 6 h at 100°C.

1-Vinyl-2-(2-furyl)-3-alkylpyrroles (IIIa-f) are high-boiling liquids with a specific weak odor and are soluble in diethyl ether, acetone, ethanol, chloroform, and dimethyl sulfoxide (DMSO) but insoluble in water. The structures of the synthesized compounds were confirmed by their IR and UV spectra (Table 2), as well as by PMR spectroscopy.

EXPERIMENTAL

The IR spectra of liquid films of the synthesized pyrroles were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in cyclohexane were recorded with a Unicam SP-8000 spectrophotometer. The PMR spectra of solutions of the compounds in CCl_4 were obtained with a Tesla BS-487C spectrometer (80 MHz) with hexamethyldisiloxane as the internal standard.

Alkyl Furyl Ketoximes Ia-f. These compounds were synthesized by a modified method [7]. A 0.14-mole sample of the alkyl furyl ketone was added to 0.2 mole of hydroxylamine hydrochloride in 40 ml of ethanol and 10 ml of water, and the mixture was stirred thoroughly with the gradual addition of 0.2 mole of sodium hydroxide in 10 ml of water in small portions. The resulting mixture was heated at 65-75°C for 2-3 h, after which it was cooled to 20°C and poured over ice. The aqueous mixture was made weakly acidic with hydrochloric acid and extracted with ether. The ether extracts were washed with water and dried with potassium carbonate. The ether was removed, and the residue was fractionated *in vacuo*. The alkyl furyl ketoximes were obtained in 75 to 82% yields.

1-Vinyl-2-(2-furyl)pyrrole (IIIa). A 6.3-g (0.05 mole) sample of oxime Ia, 1.68 g (0.03 mole) of KOH, and 100 ml of DMSO were placed in a 1-liter steel rotating autoclave, and the mixture was heated with excess acetylene (at an initial pressure of 16 atm) at 100°C for 2.5 h. It was then cooled to 20°C and diluted with 500 ml of cold water. The desired product was extracted with ether (five 50-ml portions), and the extracts were washed with water (three 100-ml portions) and dried with potassium carbonate. The ether was removed by distillation, and the residue was fractionated *in vacuo* to give 5.5 g of a mixture (bp 236-244°C) consisting of pyrrole IIa and vinylpyrrole IIIa, from which 4 g (50%) of pure vinylpyrrole IIIa was obtained by column chromatography [on L 100/250 μ silica gel with elution by hexane—ether (3:1)] (Table 1). PMR spectrum: 6.06 (4-H), 6.87 (5-H), 6.16 (3'-H), 6.25 (4'-H), 7.33 (5'-H), 4.55 (H_A), 4.96 (H_B), 7.05 (H_X), and 6.25 ppm (3-H); $J_{4,5} = 2.9$, $J_{3',4'} = 3.3$, $J_{3',5'} = 0.8$, $J_{4',5'} = 1.6$, $J_{AX} = 8.6$, $J_{BX} = 15.1$, $J_{AB} = 1.0$, $J_{3,4} = 3.4$, and $J_{3,5} = 1.7$ Hz.

2-(2-Furyl)pyrrole (IIa). A mixture (2.5 g) (bp 234-244°C) consisting of pyrrole IIa (22.4%) and vinylpyrrole IIIa (12.5%) was obtained by the method presented for vinylpyrrole IIIa from 6.3 g (0.05 mole) of ketoxime Ia, 1.2 g (0.05 mole) of LiOH, and 70 ml of DMSO. Column chromatography of this mixture gave 1.1 g of pyrrole IIa (Table 1). PMR spectrum: 6.29 (3-H), 6.08 (4-H), 6.55 (5-H), 6.18 (3'-H), 6.29 (4'-H), 7.19 (5'-H), and 8.23 ppm (NH); $J_{3,5} = 1.5$, $J_{4,5} = 2.6$, $J_{4,3} = 3.0$, $J_{5',4'} = 1.6$, $J_{5',3'} = 0.8$, and $J_{3',4'} = 3.5$ Hz.

1-Vinyl-2-(2-furyl)-3-methylpyrrole (IIIb). A mixture of 5 g (0.036 mole) of oxime Ib, 2 g (0.036 mole) of KOH, and 60 ml of DMSO was heated in a 1-liter autoclave with acetylene (at an initial pressure of 16 atm) at 130°C for 3 h. Workup as described above and vacuum distillation gave 5.3 g (85%) of vinylpyrrole IIIb (Table 1).

Vinylpyrroles IIIc, e, f were similarly synthesized (Table 1).

1-Vinyl-2-(2-furyl)-3-propylpyrrole (IIId). A 4-g (57%) sample of vinylpyrrole IIId was obtained from 5.8 g (0.035 mole) of oxime Id in the presence of 1.5 g (0.028 mole) of KOH and 70 ml of DMSO (100°C, 3 h, an initial acetylene pressure of 14 atm) (Table 1). PMR spectrum: 5.96 (4-H), 6.86 (5-H), 6.19 (3'-H), 6.34 (4'-H), 7.38 (5'-H), 4.48 (H_A), 4.90 (H_B), 6.79 (H_X), 2.33 (CH_2), 1.46 (CH_2), 0.83 (CH_3); $J_{4,5} = 2.9$, $J_{3',4'} = 3.1$, $J_{3',5'} = 0.7$, $J_{4',5'} = 1.8$, $J_{AX} = 8.8$, $J_{BX} = 15.6$, and $J_{AB} = 0.7$ Hz.

2-(2-Furyl)-3-methylpyrrole (IIb). A mixture of 5 g (0.041 mole) of oxime Ib, 2.5 g (0.045 mole) of KOH, and 100 ml of DMSO was heated to 100PC in a flask equipped with a stirrer, a reflux condenser, and a bubbler tube, and acetylene was passed into the mixture for 3 h. Another gram (0.018 mole) of KOH was then added, and the reaction mixture was refluxed for another 3 h while acetylene was bubbled through it. Standard workup gave 4.5 g of a mixture of pyrrole IIb and vinylpyrrole IIIb, from which 1.2 g (23%) of IIb and 2.5 g (40%) of IIIb were isolated by chromatography with a column filled with Al_2O_3 [elution with hexane—ether (3:1)] (Table 1).

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PREPARATION OF 1-(4-NITROPHENYL)-2-FORMYLPYRROLE FROM FURFURAL

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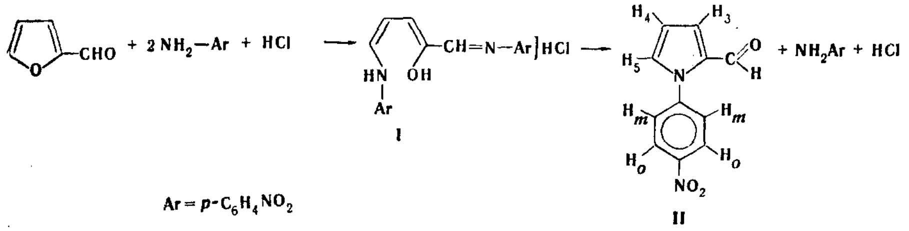
The products of the condensation of furfural with p-nitroaniline in an acidic medium in various solvents were investigated. It was established that the well-known method gives 1-(4-nitrophenyl)-2-formylpyrrole in no higher than 55% yield and 2,3-bis(4-nitrophenylamino)-2-formylpyrrole in 27% yield. A method based on a previously described method is recommended (the products are obtained in up to 72% yields).

The condensation of furfural with aromatic amines is of interest as a method for the conversion of compounds of the furan series to pyrrole derivatives. 1-(4-Nitrophenyl)-2-formylpyrrole (II) can be obtained by this method from p-nitroaniline through Stenhouse salt I [1-3]:



A method [1] involving the use of ethanol as the solvent and a method [2] that differs from the former in that methanol is used in place of ethanol and less hydrochloric acid is employed have been proposed for the synthesis of II. The Janovsky method [2] is well known; the Lüpke method [1] is described in a literature source that is difficult to obtain. In the opinion of the authors, both methods ensure quantitative yields. In the first case these yields are achieved by repeated precipitation of the reaction product after evaporation of the alcohol, while in the second case they are obtained by direct isolation of the reaction products from the reaction mixtures.

However, Petit and Pallaud [3] note the difficulties involved in the preparation of formylpyrrole II, viz., resinification and a decreased yield. Replacement of the hydrochloric acid by a cation-exchange resin did not improve the results very much [3]. The synthesis of formylpyrrole has not found wide laboratory application, although this compound is extremely promising as an intermediate for the preparation of various N-substituted pyrroles.

It is known that the reaction of furfural with aromatic amines may proceed via different pathways, depending on the synthetic conditions and the structure of the amine. The formation of pyridinium salts in addition to pyrrole derivatives is possible in an acidic medium [1, 4]; diaminocyclopentenones were obtained in a neutral medium [4]. The formation of aminopyrrolinones is also assumed [5].

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