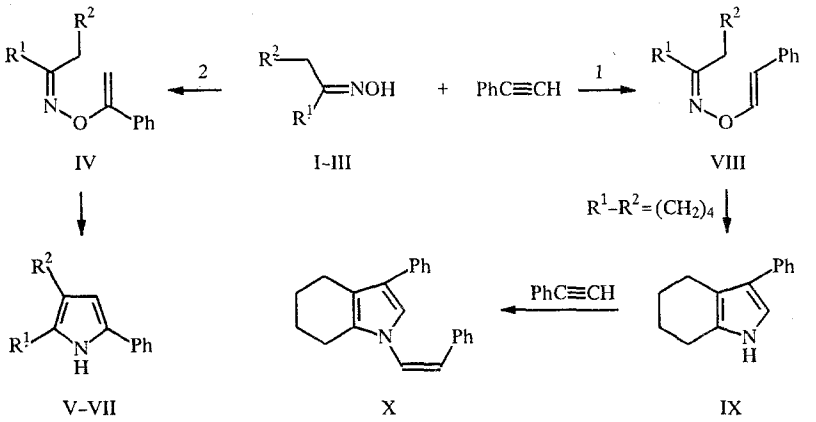
CONDENSATION OF KETOXIMES WITH PHENYLACETYLENE

S. E. Korostovka, A. I. Mikhaleva, B. A. Trofimov, S. G. Shevchenko, and M. V. Sigalov

2-Methyl-5-phenyl- and 2,5-diphenylpyrrole and 2-phenyl-, Z-[1-(2-phenylvinyl)]-3-phenyl-, and 4,5,6,7-tetrahydroindole, and 2,4-diphenyl-3,3-dimethyl-5-hydroxypyrroline have been obtained from the reaction of ketoximes with phenylacetylene, catalyzed by KOH—DMSO.

The reaction of mono- and disubstituted acetylenes with oximes has been described in a number of papers [1-5] from which no general rules have emerged. It does not usually lead to the formation of pyrroles, although its intermediate or final products are the corresponding O-vinyl derivatives of the oximes. For example, cyclohexanone oxime with cyanoacetylene gives the aminosubstituted isoxazole. The same oxime with diacetylene forms O-ethenylvinylcyclohexanone oxime, which does not lead to pyrrole on thermal decomposition [1]. From ketoximes and propargylic esters [2] or phenylthioacetylene [3], one obtains E-1-alkoxy-3-iminoxy-1-propene or 1,2-di(phenylthio)ethene, respectively, instead of the expected pyrroles. The reaction of vinylacetylene with acetoxime or cyclohexanone oxime is accompanied by the formation of the isomeric esters of these ketoximes [4]. Only the dimethyl ester of acetylenedicarboxylic acid with acetophenone and cyclohexanone oximes gives 4,5- or 2,3-dicarbomethoxypyrrole [5] via the intermediate O-α-β-dicarbomethoxyvinylketoxime. These products are not observed when these same oximes are condensed with acetylene under similar conditions [1].

Previously [6], for the purpose of testing the possibility of preparing 4- and 5-substituted pyrroles and studying the regiodirectivity of the addition of ketoximes to monosubstituted acetylene in superacid catalytic systems, we investigated the reaction of the oximes of acetone (I) and acetophenone (II) with phenylacetylene and established that under rigorous conditions (120-170°C, 5-7 h, and KOH, 30-50% of mass of ketoxime) 5-phenylsubstituted pyrroles V and VI are formed regardless of the ketoxime:phenylacetylene ratio (1:1 or 1:2). The best yield of these pyrroles was 21 and 17%, respectively. It must be noted that the reaction mass (especially in the case of ketoxime II) contained regenerated ketone (the yield of acetophenone in separate experiments reached 70%) and a number of unidentified compounds (TLC), among which it was not possible to detect 4-phenylsubstituted pyrroles (PMR). However, in a more recent paper [7] the authors realized such a possibility. On the basis of data [8, 9] concerning the predominance of β-addition of phenols to phenylacetylene under basic catalysis and the simultaneous trans-nucleophilic addition, it was proposed that the primary path of the reaction of ketoximes with phenylacetylene carried out in a superacidic medium would be path 1; i.e., the formation, ultimately, of 4(3)-phenylsubstituted pyrroles.



I, V R^1=Me, R^2=H; II, VI R^1=Ph, R^2=H; III, VII, IX, X R^1=R^2=$(CH_2)_4$

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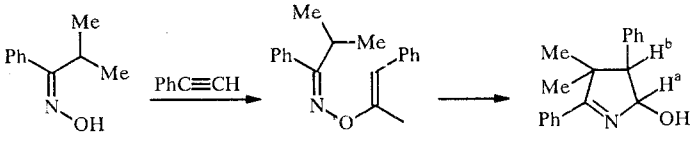
TABLE 1. IR and PMR Spectra of Phenylsubstituted Pyrroles

Pyrrole	PMR spectrum, δ, ppm	IR spectrum, ν, cm^{-1}
V*	7,8 bd (1H, s, NH); 6,22 (1H, t, 3-H, J_{14}—J_{34}=6 Hz); 5,77 (1H, t, 4-H); 2,21 (3H, s, CH_3); 7,20 (5H, m, Ph)	3430 (NH), 720 (δ CH pyrrole.), 1500, 1610 (C=C benz., pyrrole, 2860, 2930, 2979 (CH_3)
VI*	8,5 bd (1H, s, NH); 6,30 (1H, d., 3-H, 4-H, J_{13}—J_{14}=2 Hz); 7,27 (10H, m, Ph)	3440 (NH), 710 (δ CH pyrrole.), 3070, 3100 (CHbenz), 1500, 1605 (C=C benz. pyrrole.)
VII**	8,3 bd (1H, s, NH); 6,26 (1H, d, 3-H); 7,32 (5H, m, Ph); 1,80, 2,59 [8H, t, $(CH_2)_4$]	3420 (NH), 700 (δ CH pyrrole.), 1505, 1600 (C=C benz., pyrrole) 3020, 3045 (CH benz), 2835, 2920 [$(CH_2)_4$]
X***	6,78 (1H, s, 2-H); 2.75, 2,59 [4H, t, 7-H, 4-H, $(CH_2)_4$]; 1,86 [4H, t, 5-H, 6-H, $(CH_2)_4$]; 6,67 (1H, d, α-H); 6,19 (1H, d, β-H); 7,38, 7,30 (10H, m, 2Ph)	1630 (C=C NCH=CHPh), 1505, 1590 (C=Cbenz, pyrrole), 3000, 3040 (CH benz.) 680, 720 (δ CH pyrrole.), 2810, 2900, 2910 [$(CH_2)_4$]

PMR spectrum taken in: *CCl_4; **$CDCl_3$; ***acetone-d_6.

In the present work, we have established that under rather mild conditions (80°C), the primary end product of the condensation of ketoxime III with phenylacetylene is Z-[1-(2-phenylvinyl)]-3-phenyl-4,5,6,7-tetrahydroindole (X), isolated in 42% yield (based on reacted ketoxime III). Consequently, the absence of the bulky α-phenyl substituent in the 3-phenyl-4,5,6,7-tetrahydroindole (IX) forming as an intermediate, does not hinder its further reaction with phenylacetylene as it was found to do in the vinylation of 2,5-diphenylpyrrole [11]. It was not possible to isolate other compounds present in the reaction mass (TLC) because of the insignificant amounts of them present. In order to obtain 3-phenyl-4,5,6,7-tetrahydroindole, free from its 1-(2-phenyl)vinyl derivative X, ketoxime III was condensed with phenylacetylene at 96°C in a KOH/DMSO medium containing 5% water, known [11] to retard vinylation. The 22% yield of 2-phenyl-4,5,6,7-tetrahydroindole (VII), the structure of which was confirmed by the PMR spectrum (Table 1), was completely unexpected.

When a ketoxime with an aliphatic α-CH group reacts with phenylacetylene in the identical superacidic medium at a moderate temperature, one would expect the formation of the two, isomeric α- or β-phenylsubstituted O-vinyl oximes [1, 7]. It turned out that for the reaction of isopropyl phenyl ketoxime (XI) with phenylacetylene at 20-24°C in the presence of a twofold molar excess of KOH and with an equimolar ketoxime II/phenylacetylene ratio, the most favored path is 1.



XI XII XIII

As a result, 2,4-diphenyl-3,3-dimethyl-5-hydroxypyrrole (XIII) is obtained in a 7% yield. This result is evidence that the reaction follows the O-vinyl oxime mechanism. The intermediate O-(2-phenylvinyl)isopropyl phenyl ketoxime (XII) heterocyclizes even at 24°C to hydroxypyrrole XIII, but this temperature is insufficient for the dehydration of XIII to form the corresponding 3H-pyrrole.

Thus, the reaction of ketoximes with phenylacetylene makes it possible to prepare not only α- or β-phenylsubstituted pyrroles, but also their 1-(2-phenylvinyl) derivatives as well as reactive hydroxypyrroles.

EXPERIMENTAL

The IR spectra of the compounds were taken on a Specord IR-75 instrument in KBr tablets. The PMR spectra were obtained on a Tesla BS-567A (100 MHz) spectrometer in CCl_4, $CDCl_3$, or acetone-d_6 with HMDS as an internal standard.

The elementary analyses of the compounds for C, H, and N correspond to the calculated values.

2-Methyl-5-phenylpyrrole (V, $C_{11}H_{11}N$). A mixture of 3.65 g (0.05 mole) of acetoxime, 5.1 g (0.05 mmole) of phenylacetylene, 1.83 g (50% of the mass of ketoxime I) of KOH, and 50 ml of DMSO is heated in a sealed ampul at 120°C for 5 h. The reaction mass is cooled to room temperature, diluted with 3 times (by volume) the amount of water, and extracted with ether. The ethereal extracts are washed with water and dried with potassium carbonate. The ether is removed and the residue vacuum distilled to obtain 1.65 g (21%) of a fraction with T_{bp} 125°C (3 mm Hg) that crystallizes on cooling. T_{mp} 96°C.

2,5-Diphenylpyrrole (VI, $C_{16}H_{13}N$). A mixture of 10.2 g (0.075 mole) of acetophenone oxime, 7.9 g (0.077 mole) of phenylacetylene, 3.3 g (32% of the mass of ketoxime II) of KOH, and 75 ml of DMSO is heated at 170°C for 7 h in a sealed ampul. After treatment as described above, drying the ethereal extracts with $MgSO_4$ and removing the ether, the residue is vacuum distilled to isolate 2.75 g (~17%) of pyrrole VI (T_{mp} 143°C), 1 g (0.8%) of acetophenone, and 1 g of acetophenone oxime (90% conversion).

2-Phenyl-4,5,6,7-tetrahydroindole (VII, $C_{14}H_{15}N$). A mixture of 11.3 g (0.1 mole) of cyclohexanone ketoxime and 5.6 g (0.1 mole) of KOH in 50 ml of DMSO containing 2.5 ml of water is heated to 96°C. Then 4.7 g (0.046 mole) of phenylacetylene is added with stirring over a period of 1.5 h, and the mixture stirred at this temperature for another 2.5 h. The oximate is separated as a pasty mass on a funnel with a porous filter. The liquid is poured into 150 ml of water containing 1.5 g NaCl and extracted with ether. The ethereal extracts are washed with a 40% KOH solution and water and dried with potassium carbonate. The residue, after removal of ether, is vacuum distilled to obtain 2 g (22% based on starting material) of tetrahydroindole VII. It was not possible to isolate the pure compound by chromatography on a column with Al_2O_3.

Z-[1-(2-Phenylvinyl)]-3-phenyl-4,5,6,7-tetrahydroindole (X, $C_{22}H_{21}N$). A mixture of 5.6 g (0.1 mole) of KOH and 12.2 g (0.107 mole) of cyclohexanone oxime in 100 ml of DMSO is heated in a conical flask to 80°C with stirring (magnetic stirrer) and held at this temperature for 15 min. After heating has been discontinued, 20.4 g (0.2 mole) of phenylacetylene in 50 ml of DMSO is added over a 1-h period, and the mixture warmed at 80°C for 5 h, stirred without heating for another 1 h, and worked up as described in the synthesis of pyrrole V. Tetrahydroindole X is isolated in a 4.5 g (~14%) yield by chromatography on a column with Al_2O_3 (2.5:1 hexane:ether). Of the ketoxime, 8.1 g is recovered (34% conversion). T_{mp} 73-75°C. Yield of compound X, 42% (based on reacted ketoxime).

2,4-Diphenyl-3,3-dimethyl-5-hydroxypyrroline (XIII, $C_{18}H_{19}NO$). To a mixture of 2.24 g (0.04 mole) of KOH, 3.44 g (0.02 mole) of isopropyl phenyl ketoxime, and 20 ml of DMSO are added with stirring at room temperature 2.05 g (0.02 mole) of phenylacetylene and stirring is continued for 15 days (interrupted at night). The mixture is poured into 100 ml of water and extracted with ether (5 × 50 ml). The 0.5 g of crystals that precipitated are separated, boiled for 5 min in acetone, cooled, and separated from the acetone to obtain 0.4 g (7%) of hydroxypyrroline XIII 93% pure. T_{mp} 187-190°C. PMR spectrum ($CDCl_3$): 7.75 (5H, m, α-Ph); 7.30 (5H, m, β-Ph); 6.05 (1H, d.d, *a*-H, J_{ab} = 8.5 Hz); 3.12 (1H, d, b-H, J_{ab} = 8.5 Hz); 1.38 (3H, s, CH_3); 1.04 (3H, s, CH_3); 5.39 ppm (1H, , d, OH, $J_{OH,a\text{-}H}$ = 3 Hz). IR spectrum (KBr, cm^{-1}): 3180 (OH); 1100, 1130 (C—O); 1610 (C=N); 1488, 1590 (C=C in Ph); 3010, 3035, 3100 (C—H in Ph); 2825, 2860, 2910, 2950 (CH_3).

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