A NOVEL SYNTHESIS OF 3H-PYRROLES

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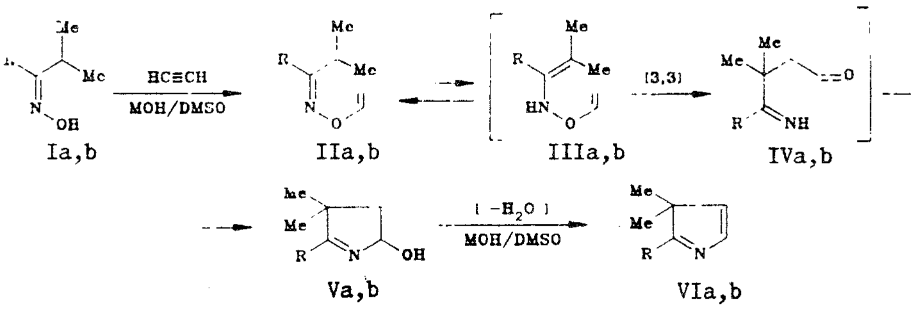
Reaction of isopropylphenyl- and isopropyl-2-thienylketoximes with acetylene, catalyzed by the system MOH (M = Na, K)-DMSO, gave 2-phenyl- and 2-(2-thienyl)-3,3-dimethyl-3H-pyrroles as well as the reaction intermediates O-vinylisopropylphenylketoxime and 2-phenyl-3,3-dimethyl-5-hydroxypyrroline. The yield of the condensation products depends on the structure of the ketoximes and the conditions for the reaction with acetylene.

3-H-Pyrroles are obtained by methods which do not differ in simplicity or feasibility [1] and, until recently, generally include non-aryl compounds [2]. When not stabilized by two substituents at position 3 they are known only as nonisolated intermediates in certain synthesis of 1H-pyrroles: the rearrangement of 2-allyl-2-methyl-3,5-diphenyl-2H-pyrroles [3] or vinylazirines [4, 5], the reaction of vinylphosphonium salts with benzonitrilemethylides [6], or of N-tritylproline methyl ester with tert-butylhypochlorite [7]. In the last ten years, 3H-pyrroles have increasingly attracted the attention of investigators [1, 8-10], in particular their use in the Diels—Alder reaction [11, 12] leading to novel skeletal condensed tetrahydropyrimidines [12]. Tetrahydropyrrolo[1,2-c]pyridines can be obtained through a 1,3-sigmatropic rearrangement of 3H-pyrroles [13].

According to our work [14], 2-phenyl-3,3-dimethyl-3H-pyrrole (VIa) can be obtained in 9% yield from isopropylphenyl ketoxime by condensation with acetylene at atmospheric pressure (70°C). Similarly, 3H-pyrroles can be obtained in 2% yield from certain piperidine oximes [15].

In this work we investigated further the reaction of acetylene with isopropylphenyl- and isopropyl(2-thienyl)ketoximes (Ia, b) in the medium MOH (M = Na, K)-DMSO and development of a preparative method for the 3H-pyrrole VIa (which is difficult to obtain) and the previously unknown 2-(2-thienyl)-3,3-dimethyl-3H-pyrrole (VIb).



I—VI a R=Ph; b R=2-thienyl; M = Na, K

In agreement with results obtained in the search for the optimum synthesis of 3H-pyrroles VIa, b (see Table 1) the yield of the 3H-pyrroles depends significantly on the structure of the other radical of the isopropyl ketoxime and the reaction conditions. At 100°C the ketoxime Ia reacts with acetylene more readily than ketoxime Ib. 3-H Pyrrole VIa is formed in 42% yield (expt. 8) but VIb in only 4% yield (expt. 10) even with prolonged reaction time (5 h, for shorter times the ketoxime Ib is recovered unchanged). When the contact time of Ia and acetylene is increased from 3 h (expt. 9) to 4 h (expt. 5) the reaction temperature can be decreased by 20°C without loss in yield (42%). The effect of continued reaction time on the yield is clearly shown in experiments 5-7. After 4 h at 90°C, using an equimolar ratio of ketoxime Ia to KOH, the 3H-pyrrole VIa is obtained in improved yield (53%, expt. 6).

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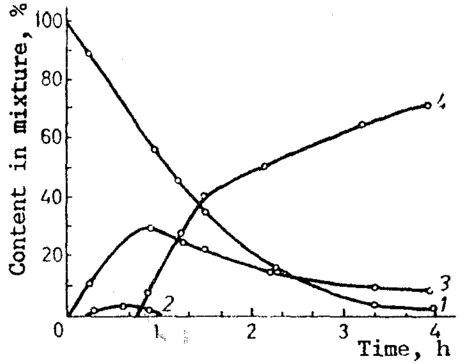

Fig. 1. Reaction of ketoxime Ia with acetylene (atmospheric pressure, 92-95°C, 4 h, equimolar ratio of ketoxime-KOH): 1) ketoxime Ia; 2) O-vinylketoxime IIa; 3) hydroxypyrroline Va; 4) 3H-pyrrole VIa.

TABLE 1. Reaction Conditions and 3H-Pyrrole Yields

Experiment[*1]	Oxime	Oxime:KOH (oxime:NaOH), mole	T, °C	Time, h	Yield[*2], %
1[*2]	Ia	1:1	40	3	37[*3]
2[*2]	Ia	1:1	50	3	23[*4]
3[*2]	Ia	1:1	100	3	31
4	Ia	1:2	80	4	42
5	Ia	1:1	90	3,5	40
6	Ia	1:1	90	4	53
7	Ia	1:1	90	5	38
8	Ia	1 : 2	100	3	42
9	Ia	(1:1,7)	100	5	26[*4]
10	Ib	1:2	100	5	4 (19)
11	Ib	1:2[*5]	100	5	11 (43)
12	Ib	1:2	110	5	7 (12)
13	Ib	1:2	125	5	3 (11)

[*1] In experiments 1-3 the initial acetylene pressure is 12 atm; in 4-13, atmospheric pressure.

[*2] Yield from theoretical, that in brackets is based on reacted ketoxime Ib.

[*3] Yield of O-vinyloxime IIa.

[*4] Yield of hydroxypyrroline Va.

[*5] With addition of Al_2O_3.

The yield of reaction product falls (Table 1) due to lower conversion of ketoxime Ia (expt. 5) and much tarring (expt. 7). The effect of temperature is more marked in the synthesis of the 3H-pyrrole VIb. Increasing it to the values given promotes a small increase in yield (compare expts. 10 and 12). Use of added Al_2O_3 (7% of the weight of the catalyst-KOH) leads to enhanced medium basicity due to its high dehydration capacity and a greater than 2.5 times increase in the yield of 3H-pyrrole VIb (expt. 11).

The reaction with acetylene under pressure (12 atm) at 100°C is accompanied by polymerization of both starting material and product. This hinders isolation of the 3H-pyrroles in good yields (expt. 3). At lower temperatures it was possible to stop the condensation of ketoxime Ia with acetylene at the intermediate stages. At 40°C the main product is O-vinylisopropylphenyl ketoxime (IIa) (37%, expt. 1) and at 50°C 2-phenyl-3,3-dimethyl-5-hydroxypyrroline (Va) (23%, expt. 2). At atmospheric pressure Va can be synthesized in practically the same yield at increased temperature (100°C) using NaOH-DMSO (expt. 9).

We have used GLC to study the reaction of Ia with acetylene at atmospheric pressure and 92-95°C (see Fig. 1). In the figure it can be seen that ketoxime Ia has fully reacted after 4 h (curve 1), the intermediate O-vinylketoxime IIa (curve 2) rapidly rearranges to the hydroxypyrroline Va (curve 3) which loses water converting to the 3H-pyrrole VIa approximately 40 min after the start of the reaction (curve 4). The content of VIa in the final reaction mixture reaches 70%.

Thus Trofimov reaction conditions can be used to convert ketoximes with an aliphatic α-CH group to 2-aryl(hetaryl)-3H-pyrroles (VI) by a hetero-Claisen type rearrangement of the intermediate O-vinylketoxime (II) which first prototropically isomerizes to O,N-divinylhydroxylamine III.

EXPERIMENTAL

GLC was used to monitor the reaction progress and compound purities. The chromatograph was a Tsvet 100 with a 0.8 m × 3 mm column, Chromaton N-AW support, XE-60 silicone liquid phase, helium carrier, thermostat temperature 90-170°C (V = 8°C/min), and vaporization temperature 240°C. IR spectra were recorded on a Specord-75 instrument for thin layers or KBr tablets. PMR spectra were obtained on a Tesla BS-567A spectrometer (100 MHz).

O-Vinylisopropylphenylketoxime (IIa, $C_{12}H_{15}NO$). A mixture of ketoxime Ia (16.3 g, 0.1 mole), KOH (5.6 g, 0.1 mole), and DMSO (200 ml) was held for 3 h at 40°C in a 1-liter rotary steel autoclave under acetylene pressure (initially 12 atm). The product was diluted with water (700 ml) and extracted with ether (3 × 100 ml). The ether extract was washed with water, dried with potassium carbonate, and the residue fractionated in vacuo to give the O-vinylketoxime (7 g, 37%) with bp 80-82°C (2.66 HPa), d_4^{20} 0.9667, n_D^{20} 1.5282. PMR spectrum ($CDCl_3$): 1.20 (6H, d, $CH(CH_3)_2$); 3.52 (1H, m, $CH(CH_3)_2$); 7.37 (5H, m, Ph); 4.13 (1H, q, β-H_{cis}, $^2J = 2.5$, $^3J = 6.0$ Hz); 4.61 (1H, q, β-H_{trans}, $^3J = 14.0$ Hz); 6.99 ppm (1H, q, α-H). IR spectrum (film): 1612 (C=C, $OCH{=}CH_2$); 1485, 1598 (C=C, Ph); 3030 (CH, Ph); 2850, 2910, 2945 (HC sp^3 CH_3); 1160 (ν^{as} C—O—N); 970 cm^{-1} (N—O).

2-Phenyl-3,3-dimethyl-5-hydroxypyrroline (Va, $C_{12}H_{14}NO$). A. Ketoxime Ia (16.3 g, 0.1 mole), KOH (5.6 g, 0.1 mole), and DMSO (200 ml) were heated in a liter autoclave under acetylene pressure (initially 12 atm) at 50°C for 3 h. The reaction product was diluted with water and extracted with ether. The abstracts were washed with water and dried (potassium carbonate). After removal of ether the crystals were separated from the liquid and washed with ether. Recrystallization from 50% ethanol gave the hydroxypyrroline Va (4.32 g, 23%), identical in melting point, IR UV, PMR, and mass spectrometry to that reported in [17]. The remaining liquid (12 g) was column chromatographed on Al_2O_3 using hexane—ether eluent (3:1) to give O-vinylketoxime IIa (0.13 g, 0.7%) and ketoxime Ia (9.5 g).

B. Ketoxime Ia (4.08 g, 0.025 mole), NaOH (1 g, 0.043 mole) and DMSO (50 ml) were heated at 100°C for 5 h passing acetylene with continuous stirring. Workup as in method A gave Va (1.22 g, 26%) and Ia (1.5 g).

2-Phenyl-3,3-dimethyl-3H-pyrrole (VIa, $C_{12}H_{13}N$). Ketoxime Ia (4.08 g, 0.025 mole), KOH (1.4 g, 0.025 mole), and DMSO (50 ml) were heated at 90°C for 4 h with stirring and passage of acetylene at atmospheric pressure. Treatment with water, extraction with ether, drying over potassium carbonate, and fractionation on an alumina column (hexane—ether, 6:1) gave the 3H-pyrrole VIa (2.27 g, 53%) with bp 88-96°C (1.33 GPa). The density, refractive index, mass spectrum, IR, and PMR spectrum were identical to those reported in [16].

2-(2-Thienyl)-3,3-dimethyl-3H-pyrrole (VIb, $C_{10}H_{11}NS$). A mixture of ketoxime Ib (4.23 g, 0.025 mole), KOH (2.8 g, 0.050 mole), and Al_2O_3 (0.2 g) in DMSO (50 ml) was heated at 100°C for 5 h with constant stirring and passage of acetylene. Treatment as above and chromatography on Al_2O_3 (hexane—ether, 6:1) gave 3H-pyrrole VIb (0.51 g, 11%) with d_4^{20} 1.0958 and n_D^{20} 1.5984. PMR spectrum ($CDCl_3$): 1.39 (6H, s, $2CH_3$); 6.20 (1H, d, 4-H); 6.99 (1H, d, 5-H, $^3J_{45}$ = 3.2 Hz); 7.46 (1H, d, 5'-H); 7.41 (1H, d, 3'-H); 7.13 ppm (1H, q, 4'-H). IR spectrum (thin layer): 1360, 1380 (*gem*-dimethyl group); 2840, 2905, 2950 (sp^3 CH); 1495, 1590 (ring C=C); 3055, 3080 (ring CH); 1650 cm^{-1} (C=N); absorption at 3200-3600 cm^{-1} absent. Mass spectrum: M$^+$ 177. Ketoxime Ib (3.1 g) was also isolated.

Elemental analytical data for the compounds agreed with that calculated.

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