

Selective Synthesis of 1-Vinylpyrroles Directly from Ketones and Acetylene: Modification of Trofimov Reaction

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Received December 24, 2005

Abstract—Consecutive treatment of ketones with a system $\text{NH}_2\text{OH}\cdot\text{HCl}$ – NaHCO_3 –DMSO and acetylene excess in the presence of KOH (100–120°C, initial acetylene pressure 12–15 at) led to a selective formation of 2- and 2,3-substituted 1-vinylpyrroles in 51–79% yields. Ketones of aliphatic, cycloaliphatic, aromatic, heteroaromatic, and tetrahydronaphthalene series were involved into the reaction.

DOI: 10.1134/S1070428007020133

Pyrrole structures appear in many biologically important compounds and also are precursors of materials for opt electronics, synthetic metals, and sensors, therefore the number of publications on the new methods of building up pyrrole ring incessantly grows. However many among studies on pyrrole synthesis require difficultly available reagents and catalysts [1–12].

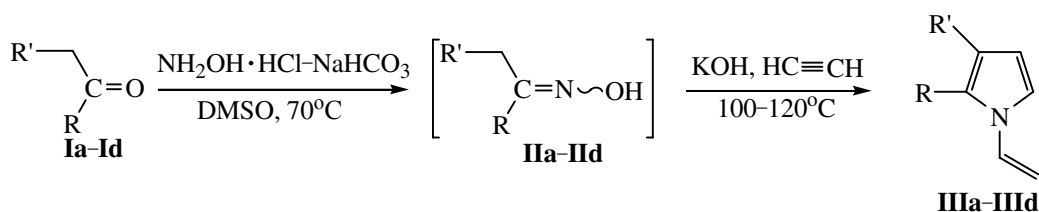
One of the few simple methods convenient for industrial implementation providing pyrroles with alkyl, aryl, and hetaryl substituents from available initial compounds (ketoximes and acetylene) is Trofimov reaction [13–17]. This is the only one among the known procedures that makes it possible a one-pot preparation not only of versatile 2- and 2,3-substituted pyrroles but also of their N-vinyl derivatives, valuable pyrrole building blocks and monomers. We reported recently in a short communication [18] on a fundamental possibility to use in Trofimov reaction instead of ketoximes of more accessible and cheap ketones. It was shown that ketones

reacted with hydroxylamine and acetylene under atmospheric pressure in the presence of the system KOH–DMSO giving mixtures of pyrroles and 1-vinylpyrroles. The goal of further investigations was increasing the process selectivity with respect to the most valuable products, 1-vinylpyrroles.

The target was achieved by application of acetylene excess under pressure.

The selective synthesis of 1-vinylpyrroles (see table, Scheme 1) was carried out as follows: A mixture of the ketone, $\text{NH}_2\text{OH}\cdot\text{HCl}$, and NaHCO_3 in DMSO heated to 70°C was flushed with argon, KOH was added, and the reaction mixture was treated with acetylene in a pressure reactor at 100–120°C. The initial acetylene pressure was the same as that in the gas cylinder. The maximum pressure at the reaction temperature was 25–35 at and fast decreased. At the reaction completion (3 h) the pressure was 13–15 at, and on cooling of the reaction mixture, 2–4 at.

Scheme 1.



R = R' = Me (a); R, R' = $(\text{CH}_2)_4$ (b); R' = H, R = Ph (c), 2-thienyl (d). = R' = Me (a); R, R' = $(\text{CH}_2)_4$ (b); R' = H, R = Ph (c), 2-thienyl (d).

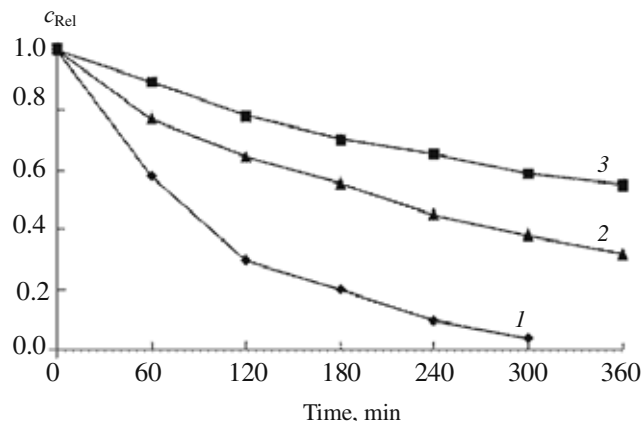
Reaction conditions and yields of 1-vinylpyrroles

Compd. no	Temperature, °C	Yield, %
IIIa	101–108	52
IIIb	100–103	64
IIIc	106–112	71
IIId	116–121	51
IIIe	100–106	79

To establish the applicability range of the new version of Trofimov reaction we tested ketones **Ia–Id** of aliphatic, cycloaliphatic, aromatic, and heteroaromatic series. The preparative yield of 1-vinylpyrroles **IIIa–IIId** attained 51–71% (see table). Here the heating conditions (100–120°C) and the time of reaction (3 h) favorably distinguish from those described for pyrroles synthesis from ketoximes (for instance, with pyrrole **IIId**, 130–140°C, 6–8 h)[19].

The new pyrrole synthesis was also successfully extended to ketones of hydronaphthalene series. 1-Vinyl-4,5-dihydrobenzo[*g*]indole **IIIe** was obtained from 1-tetralone (**Ie**) in 79% yield (Scheme 2, table).

Prior to this study the possibility to use DMSO as a solvent in ketones oximation was not apparent because sufficient kinetic and experimental data were lacking for evaluation of its characteristics as compared to other solvents. DMSO was applied to oximation of carbonyl groups in lignines with a mixture of hydroxylamine hydrochloride and triethanolamine [20]. Compared with the “classic” method (aqueous ethanol, 25°C, 30 h) [21] in DMSO (80°C, 2 h) the reaction went to completion due to total solubility of lignine. Nonetheless the ketoximes are commonly prepared with the use of ethanol and pyridine [22, 23]. Therefore we evaluated the oximation rates of ketones under comparable conditions in DMSO, ethanol, and pyridine. It turned out that methyl ethyl ketone (**Ia**) and cyclohexanone (**Ib**) in all three solvents at room temperature underwent complete oximation within several minutes, whereas acetophenone (**Ic**) in DMSO even at 70°C in 6 h was converted into the oxime only to 45%



Time dependence of relative acetophenone concentrations (dimensionless units) in ethanol (1), pyridine (2), and DMSO (3) at 70°C (10 wt% of acetophenone, 5 wt% of hydroxylamine hydrochloride, 5 wt% of water).

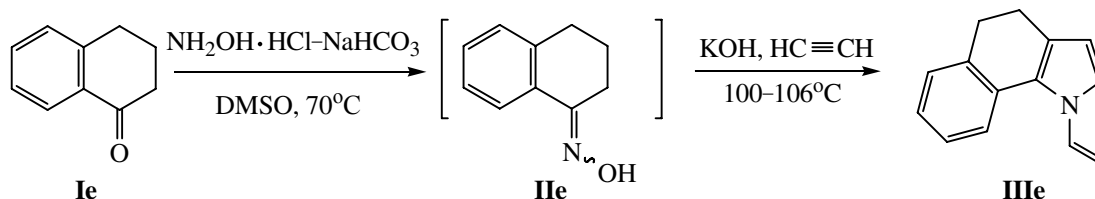
(see figure): The ratio of oximation rates in DMSO, pyridine, and ethanol was 1.0:2.1:3.8 respectively (GLC monitoring).

As shows sufficiently high yield of 1-vinyl-pyrrole **IIIc** (see table), additional oximation of acetophenone occurs in the course of the main process at higher temperature. We proved experimentally, that at 95°C the oximation of acetophenone (**Ic**) in DMSO was complete in 45 min. Our results demonstrated that DMSO is a plausible solvent for oximation of ketones.

The use of NaHCO₃ as a base for isolation of free hydroxylamine from the salt NH₂OH·HCl instead of alkali (KOH) prevented the condensation and methylenation processes in the initial ketones possible in the KOH–DMSO system [24].

Hence we developed a new version of Trofimov reaction providing a possibility of a selective preparation of 1-vinylpyrroles directly from ketones. By kinetic experiments DMSO was demonstrated to be a plausible solvent for preparation of intermediate ketoximes. Avoiding the stages of preparative production, isolation, and purification of ketoximes is an obvious advantage of the method developed which can be interesting for many researchers specialized in pyrrole chemistry.

Scheme 2.



EXPERIMENTAL

^1H (400.13 MHz) and ^{13}C (101.61 MHz) NMR spectra were registered on a spectrometer Bruker 400-DPX in CDCl_3 , internal reference HMDS. IR spectra were recorded on Bruker ISF-25 instrument.

General procedure of 1-vinylpyrroles synthesis from ketones and acetylene. A mixture of 10.4 g (0.15 mol) of $\text{NH}_2\text{OH}\cdot\text{HCl}$ and 12.6 g (0.15 mol) of NaHCO_3 was dissolved at stirring in 200 ml of DMSO, and then 0.15 mol of ketone was added. The mixture was heated at 70°C for 3 h. At the beginning of the process strong CO_2 liberation was observed. The hot reaction mixture was flushed with argon to remove CO_2 and then it was charged into a steel rotating pressure reactor of 1 liter capacity, thereto 12.4 g (0.19 mol) of $\text{KOH}\cdot 0.5\text{H}_2\text{O}$ was added, and acetylene was supplied to saturation (initial pressure 12–15 at). The reactor was heated to the required reaction temperature and the heating was maintained for 3 h (see the table). After discharge from the reactor the mixture was diluted with water (400 ml), and the product was extracted into ether (6×100 ml). The ether extract was washed with water (3×100 ml) and dried with K_2CO_3 . The ether was distilled off, the residue was purified by flash-chromatography (Al_2O_3 , eluent hexane). The physical constants and ^1H , ^{13}C , and IR spectra of 1-vinylpyrroles obtained were consistent with the published data [13].

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 03-03-32472) and of the Presidium of the Russian Academy of Sciences (grants nos. 10002-251/P-25/155-305/200404-072 and 10104-71/P-25/155-305/090605-003).

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