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First Example of Favorskii Ethynylation of Pyrrolecarbaldehydes: Synthesis of 1-(1-Methyl-1*H*-pyrrol-2-yl)prop-2-yn-1-ol

L. N. Sobenina, O. V. Petrova, D. N. Tomilin, A. V. Ivanov, V. S. Shcherbakova, A. I. Mikhaleva, and B. A. Trofimov

Favorskii Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences, ul. Favorskogo 1, Irkutsk, 664033 Russia
e-mail: boris_trofimov@irioch.irk.ru

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Abstract—1-(1-Methyl-1*H*-pyrrol-2-yl)prop-2-yn-1-ol has been synthesized for the first time by ethynylation of 1-methyl-1*H*-pyrrole-2-carbaldehyde with acetylene in the superbasic system KOH–DMSO–H_2O under atmospheric pressure.

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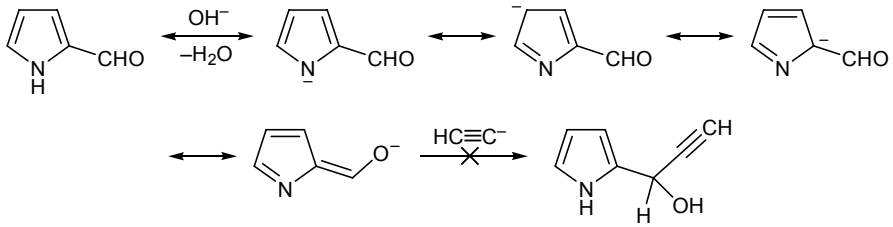
Propargyl alcohols derived from pyrrolecarbaldehydes and acetylenes are important synthetic intermediates that are increasingly used in drug design [1–6]. For example, they are used in the synthesis of protein kinase inhibitors and modulators [1] and as building blocks in the preparation of anti-inflammatory drugs, in particular for the treatment of rheumatoid arthrosis [2]. Some compounds of this series have recently been patented [3] as starting compounds for the synthesis of EDG-1 receptor antagonists that are efficient in the prophylactics and treatment of inflammatory processes and diseases related to anomalous angiogenesis, hypertensive cerebral crisis, brain ischemia, malignant tumors, cerebral and myocardial infarctions, nephritises, pneumonia, immune disorders, Crohn's diseases, colitises, and chronic diarrhea.

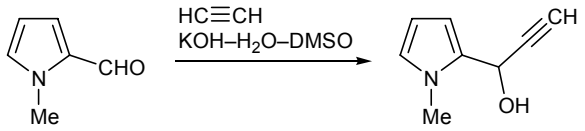
1-(Pyrrol-2-yl)prop-2-yn-1-ols are commonly synthesized [4–6] by reaction of pyrrolecarbaldehydes with alkynylmagnesium halides (Iotsitch reagents) since the classical Favorskii reaction (ethynylation of carbonyl compounds with acetylenes in the presence of potassium hydroxide) with aromatic and heteroaromatic aldehydes was considered to be inefficient [7–9]. Only recently we succeeded in developing a specific version of the Favorskii reaction, which made it possible to obtain secondary acetylenic alcohols in 46–67% yield from aromatic and heteroaromatic aldehydes as well [10, 11]. The developed procedure is based on the use of the heterogeneous catalytic system KOH–H_2O–DMSO. Here, reduction of the basicity of the system via controllable addition of water prevented acetylene–allene isomerization and subsequent transformations of the resulting secondary acetylenic alcohol.

However, this new modification of the Favorskii reaction turned out to be inapplicable to ethynylation of pyrrolecarbaldehyde. In fact, no expected propargyl alcohol was obtained from 1*H*-pyrrole-2-carbaldehyde (the initial compound was completely recovered from the reaction mixture) under the conditions ensuring

Scheme 1.



Scheme 2.



1 **2**

successful synthesis of secondary acetylenic alcohols from furfural and thiophene-2-carbaldehyde [10]. Presumably, this is the result of intramolecular negative charge transfer from the ionized pyrrole fragment to the carbonyl group, which considerably reduces electrophilicity of the latter (Scheme 1).

Taking the above stated into account, we believed that 1-substituted pyrroles in which proton abstraction from the nitrogen atom is impossible should react with acetylene according to the conventional scheme to produce secondary acetylenic alcohols [10]. This assumption was confirmed completely. The reaction of 1-methyl-1*H*-pyrrole-2-carbaldehyde (**1**) with acetylene in a suspension of KOH in DMSO/H_2O afforded the expected propargyl alcohol **2** in 62% yield (calculated on the reacted aldehyde **1** whose conversion was 50%, Scheme 2). The reaction was carried at a KOH–H_2O–DMSO molar ratio of 1:4.5:11 in a stream of acetylene under atmospheric pressure at –5 to –7°C (3 h). Unreacted pyrrolecarbaldehyde **1** was removed from the reaction mixture by extraction with hexane.

Thus, we were the first to demonstrate that appropriate version of the Favorskii reaction can be successfully used to synthesize secondary acetylenic alcohols from 1-substituted 1*H*-pyrrole-2-carbaldehydes. The discovered reaction opens new prospects in the development and practical application of pharmacologically important 1-(1*H*-pyrrol-2-yl)prop-2-yn-1-ols.

EXPERIMENTAL

The spectral and analytical data were obtained using the equipment of the Baikal Joint Analytical Center, Siberian Branch, Russian Academy of Sciences. The ^1H and ^{13}C NMR spectra were recorded on a Bruker 400DPX spectrometer at 400.13 and 100.61 Hz, respectively, using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. The elemental analysis was obtained on a Thermo Finnigan 1112 elemental analyzer. All initial reagents and solvents were commercial products.

1-(1-Methyl-1*H*-pyrrol-2-yl)prop-2-yn-1-ol (2). A mixture of 30 mL of DMSO, 2.38 g (36 mmol) of potassium hydroxide, and 3 mL (10% relative to DMSO) of water was cooled to –5 to –7°C, and acetylene was passed through that mixture over a period of 30 min under stirring. A solution of 2.0 g (18 mmol) of 1-methyl-1*H*-pyrrole-2-carbaldehyde (**1**) in 10 mL of DMSO was added dropwise over a period of 1.5 h while continuing passing acetylene and stirring. When the addition of **1** was complete, acetylene was passed through the mixture for 1.5 h more. According to the ^1H NMR data, the mixture contained compound **1** (50% of the initial amount) which was removed by extraction with hexane (5 × 30 mL) at 12–14°C, whereas the main part of product **2** remained in aqueous DMSO. The hexane extracts were combined and washed with water, and the aqueous washings were combined with the aqueous DMSO fraction diluted with water (1:2) and extracted with diethyl ether (5 × 30 mL). The extract was washed with water, dried over Na_2SO_4, and evaporated, and the oily residue was passed through a layer of alumina using hexane as eluent. Yield 0.74 g (62% on the reacted aldehyde **1**). IR spectrum, ν, cm^{-1}: 3368, 3280, 1628, 1601, 1490, 1473, 1329, 1249, 1019, 891, 812, 748, 730, 628. ^1H NMR spectrum, δ, ppm: 2.12 br.s (1H, OH), 2.60 d (1H, ≡CH, J = 2.3 Hz), 3.79 s (3H, NMe), 5.45 d (1H, C**H**OH, J = 3.2 Hz), 6.03 m (1H, 3-H), 6.30 m (1H, 4-H), 6.61 m (1H, 5-H). ^{13}C NMR spectrum, δ_C, ppm: 132.0, 124.4, 108.8, 106.6, 82.1, 73.7, 57.5, 34.1. Found, %: C 81.42; H 5.54; N 5.99. $C_{16}H_{13}NO$. Calculated, %: C 81.68; H 5.57; N 5.95.

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