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*Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 80th anniversary*

# Improved Synthesis of Tertiary Propargyl Alcohols by the Favorskii Reaction of Alkyl Aryl (Hetaryl) Ketones with Acetylene

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**Abstract**—Alkyl aryl (hetaryl) ketones react with acetylene under atmospheric pressure in the superbasic system KOH–EtOH–$H_2O$–DMSO at 10–15°C (2 h) to give the corresponding tertiary propargyl alcohols in up to 91% yield. The procedure requires no large excess of KOH and low-boiling inflammable solvents, produces few wastes, and is safe and convenient on the laboratory scale; there are no limitations for its large-scale application.

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Propargyl alcohols are widely used in fine and large-scale organic synthesis as starting compounds for the preparation of acetylenic ethers [1, 2], unsaturated ketones [3, 4], and heterocycles [5, 6]. They are also used in the synthesis of isoprenoids (including large-scale manufacture of isoprene) [7], carotenoids [8], vitamins A and E [9], fragrant compositions [10], acaricides, herbicides, corrosion inhibitors, non-ionic surfactants (surfynols) [8, 11], and substituted indenes [12, 13].

The synthesis of propargyl alcohols from acetylene and ketones of the aliphatic and cycloaliphatic series according to the Favorskii reaction [14] generally involves no experimental difficulties and ensures almost quantitative yields, whereas more readily enolizable alkyl aryl (hetaryl) ketones difficultly react with acetylene under analogous conditions, and the yields of their ethynylation products are usually poor [15]. In order to enhance the reaction efficiency, it is necessary to increase pressure, which reduces the safety of the process and requires considerably complicated equipment. In some cases, more complex versions of the Favorskii reaction were applied. For instance, Iotsitch complexes [16], alkali metal acetylides in liquid ammonia [17], tetrahydrofuran [18], or diethyl ether [19], sodium ethynyl(trimethyl)aluminate [20], or lithium acetylide–ethylenediamine complex [21] were used as ethynylating agents.

Blumental [22] described the synthesis of tertiary propargyl alcohol from acetophenone and acetylene in the presence of powdered potassium hydroxide with a rigorously defined grain size (100 mesh) in DMSO or ethylenediamine (yield 39 and 57%, respectively). When the reaction was carried out in DMSO, the product was not isolated as individual substance but as a mixture of propargyl alcohol and the corresponding diol (20%). Poor yield of the target product, low selectivity, and the necessity of using rigorously defined grain size fraction of KOH and highly toxic ethylenediamine as solvent did not allow wide application of this procedure in preparative practice.

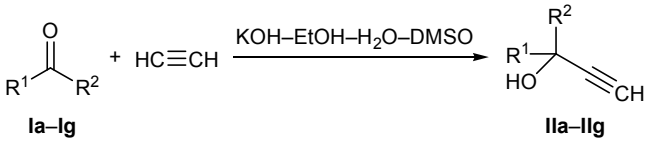
Up to now, the most efficient is the procedure for the synthesis of tertiary propargyl alcohols (~90% yield) from alkyl aryl ketones and acetylene according to the Nazarov version of the Favorskii reaction [23]. The reactions were carried out under an acetylene pressure of 8–10 atm in anhydrous diethyl ether at 15–20°C in the presence of KOH (4–6 equiv with respect to the initial ketone) with addition of ethanol (1 vol % with respect to the solvent). The reactions were slow (5–6 h), the conversion of the initial ketone was not always complete, and the selectivity was not suffi-

ciently high (up to 5% of the corresponding acetylenic diol was formed). Furthermore, the necessity of continuous supply of acetylene and ketone under pressure and the use of flammable solvent and large excess of alkali hamper laboratory application of this procedure and considerably complicate its large-scale implementation.

While performing systematic studies on ethynylation of alkyl aryl (hetaryl) ketones with acetylene in superbasic medium we found conditions that allowed us to radically improve the efficiency of synthesis of tertiary propargyl alcohols.

Ketones **Ia**–**Ig** readily reacted with acetylene under atmospheric pressure in the superbasic catalytic system KOH–EtOH–$H_2O$–DMSO at 10–15°C over a period of 2 h to give propargyl alcohols **IIa**–**IIg** in 64–91% yield (Scheme 1). The reaction was highly selective, and only in a few cases traces of acetylenic diols were detected in the crude products by $^1$H NMR spectroscopy.

**Scheme 1.**

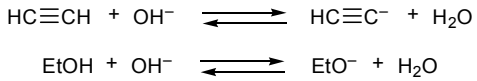



$R^1$ = Ph, $R^2$ = Me (**a**); $R^1$ = Ph, $R^2$ = Pr (**b**); $R^1$ = 3-MeO-$C_6H_4$, $R^2$ = Me (**c**); $R^1$ = naphthalen-2-yl, $R^2$ = Me (**d**); $R^1$ = pyridin-4-yl, $R^2$ = Me (**e**); $R^1$ = furan-2-yl, $R^2$ = Me (**f**); $R^1$ = thiophen-2-yl, $R^2$ = Me (**g**).

The optimal molar ratio of the components (**I**–KOH–EtOH–$H_2O$) determined from the results of a number of experiments was 1 : 1 : 0.5 : 0.5, and the optimal concentration of ketones **I** in DMSO was 2–3 M. Commercial DMSO containing 0.1–0.5% of water was used without preliminary purification. A homogeneous reaction mixture was saturated with acetylene, and the concentration of the latter was maintained constant throughout the process by continuously bubbling it through the solution (flow setup).

Obviously, the efficiency of the proposed procedure is determined by enhanced catalytic activity of the superbasic system and change of physicochemical parameters of the medium due to the use of potassium hydroxide hemihydrate (KOH·0.5$H_2O$) and increased concentration of ethanol (as compared to [23]). These conditions give rise to an equilibrium homogeneous catalytic system including potassium cations and hydroxide, ethoxide, and acetylenide anions (Scheme 2).

**Scheme 2.**

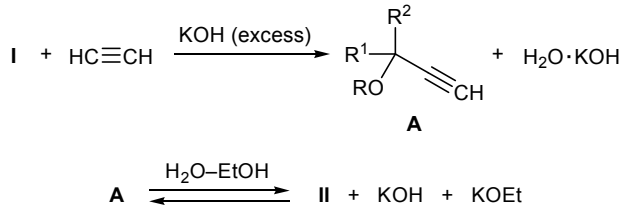


Owing to complete dissolution of potassium hydroxide in the reaction medium, not only the concentration of base in solution but also its nature change: the activity of anions, including acetylide ions, sharply increases due to their weak solvation in DMSO (superbasic effect [24]). The reactivity of undissociated potassium hydroxide molecules also increases as a result of loosening of KOH ion pairs (according to quantum-chemical calculations, the K–O bond becomes longer [25]).

The Favorskii reaction is generally carried out using a large excess of powdered KOH in an anhydrous solvent. Initially, the corresponding acetylenic alcoholate is formed, for the liberated water is bound with alkali in the solid phase; i.e., the reaction is noncatalytic.

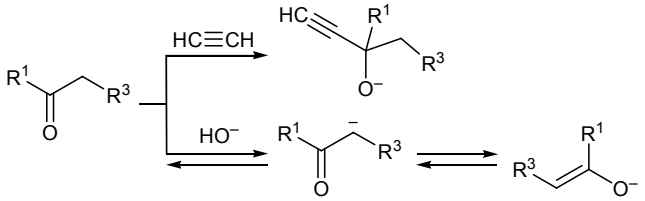
If only 1 equiv of KOH and 0.5 equiv of water and ethanol are used per equivalent of ketone **I** (see above), alcoholate **A** is converted into propargyl alcohol **II** by the action of water and ethanol (Scheme 3), and the reactions becomes catalytic.

**Scheme 3.**




This is confirmed by the fact that ethynylation of ketone **Ia** with acetylene in the presence of 0.5 equiv of KOH takes 4.5 h and gives propargyl alcohol **IIa** in 78% yield (isolated product), the conversion of **Ia** being 84%. Furthermore, superbasic medium accelerates prototropic processes such as enolization, so that nucleophilic addition of acetylide ion to the carbonyl

**Scheme 4.**



R = H, Alk.

group (ethynylation) should not be limited by the reversible enolization (Scheme 4).

Significant preparative advantages of the proposed procedure are experimental simplicity (atmospheric pressure), replacement of diethyl ether by fire- and explosion-safe dimethyl sulfoxide, and considerable reduction of the amount of KOH. Therefore, the procedure is promising for use not only in research laboratory but also for enlarged syntheses, and tertiary propargyl alcohols containing aryl and hetaryl substituents become really accessible from alkyl aryl (hetaryl) ketones and acetylene.

## EXPERIMENTAL

The IR spectra were recorded on a Bruker Vertex 70 spectrometer from samples prepared as films or KBr pellets. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DPX 400 instrument (400.13 and 100.61 MHz, respectively) at room temperature using hexamethyldisiloxane as internal standard (δ 0.05 ppm). The elemental compositions were determined on a Flash EA 1112 analyzer. The melting points were measured on a Kofler hot stage.

**Tertiary propargyl alcohols IIa–IIg (*general procedure*).** A 100-ml round-bottom flask equipped with a magnetic stirrer and a gas-inlet tube was charged with a mixture of 10.0 g (0.15 mol) of KOH·0.5$H_2O$ and 5 ml (0.09 mol) of ethanol in 50 ml of DMSO. The mixture was heated to 110°C under stirring over a period of 30 min until it turned homogeneous. The mixture was then cooled to 15°C and saturated with acetylene by passing it therethrough over a period of 30 min. A solution of 0.15 mol of ketone **Ia–Ig** in 10 ml of DMSO was added dropwise over a period of 1 h while continuously bubbling acetylene, and the mixture was stirred for 1 h under a stream of acetylene. The mixture was then diluted with a cold (7–10°C) solution of 16.5 g of ammonium chloride in 100 ml of water and extracted with diethyl ether (3×20 ml), the extracts were washed with water (3×10 ml), dried over $MgSO_4$, and evaporated, and the crude product was purified by column chromatography on neutral alumina using hexane as eluent.

**2-Phenylbut-3-yn-2-ol (IIa).** Yield 20.52 g (91%), colorless crystals, mp 43–47°C; published data [23]: mp 49°C. IR spectrum, ν, cm$^{-1}$: 3288, 2983, 2929, 1489, 1448, 1366, 1225, 1151, 1091, 1054, 933, 766, 701, 660, 586. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.70 s (3H, $CH_3$), 2.58 s (1H, 4-H), 2.74 s (1H, OH), 7.22 m (1H, 4′-H), 7.28 m (2H, 3′-H, 5′-H), 7.58 m (2H, 2′-H, 6′-H). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 32.8 ($C^1$), 69.5 ($C^2$), 72.7 ($C^4$), 86.7 ($C^3$), 124.3 ($C^{2'}$, $C^{6'}$), 127.3 ($C^{4'}$), 124.3 ($C^{3'}$, $C^{5'}$), 144.3 ($C^{1'}$). Found, %: C 81.93; H 6.56. $C_{10}H_{10}O$. Calculated, %: C 82.16; H 6.89.

**3-Phenylhex-1-yn-3-ol (IIb).** Yield 18.20 g (68%), yellow oily substance. IR spectrum, ν, cm$^{-1}$: 3410, 3303, 3062, 2961, 2873, 2113, 1954, 1888, 1812, 1680, 1600, 1489, 1449, 1379, 1317, 1203, 1139, 1110, 1030, 948, 609, 169, 700, 657, 584. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.84–0.88 m (3H, $CH_3$), 1.28–1.52 m (2H, 5-H), 1.79–1.95 m (2H, 4-H), 2.53 s (1H, OH), 2.64 s (1H, 1-H), 7.26–7.25 m (1H, 4′-H), 7.32–7.30 m (2H, 3′-H, 5′-H), 7.59–7.58 m (2H, 2′-H, 6′-H). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 13.9 ($C^6$), 17.9 ($C^5$), 47.4 ($C^4$), 73.2 ($C^3$), 74.0 ($C^1$), 86.4 ($C^2$), 125.4 ($C^{2'}$, $C^{6'}$), 127.7 ($C^{4'}$), 128.1 ($C^{3'}$, $C^{5'}$), 144.2 ($C^{1'}$). Found, %: C 82.53; H 8.14. $C_{12}H_{14}O$. Calculated, %: C 82.72; H 8.10.

**2-(3-Methoxyphenyl)but-3-yn-2-ol (IIc).** Yield 24.36 g (90%), yellow oily substance. IR spectrum, ν, cm$^{-1}$: 3419, 3290, 2987, 2936, 2837, 2113, 1675, 1600, 1486, 1452, 1363, 1289, 1152, 1078, 1043, 936, 879, 817, 786, 702, 651, 546. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.65 s (3H, $CH_3$), 2.21 s (1H, 4-H), 2.61 s (1H, OH), 3.31 s (3H, $OCH_3$), 6.66–6.64 m (1H, 4′-H), 7.04–7.02 m (1H, 6′-H), 7.25–7.23 m (1H, 2′-H), 7.32–7.31 m (1H, 5′-H). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 33.4 ($C^1$), 54.7 ($OCH_3$), 69.6 ($C^2$), 72.7 ($C^4$), 87.8 ($C^3$), 111.1 ($C^{2'}$), 113.2 ($C^{4'}$), 117.6 ($C^{6'}$), 129.3 ($C^{5'}$), 147.5 ($C^{1'}$), 160.0 ($C^{3'}$). Found, %: C 74.69; H 6.70. $C_{11}H_{12}O_2$. Calculated, %: C 74.98; H 6.86.

**2-(Naphthalen-2-yl)but-3-yn-2-ol (IId).** Yield 26.22 g (87%), yellow oily substance. IR spectrum, ν, cm$^{-1}$: 3537, 3394, 3293, 3057, 2986, 2930, 2113, 1923, 1670, 1629, 1600, 1570, 1445, 1368, 1272, 1220, 1187, 1128, 1080, 1051, 953, 934, 860, 820, 749, 669, 566, 478. $^1$H NMR spectrum ($CDCl_3$), δ ppm: 1.69 s (3H, $CH_3$), 2.22 s (1H, 4-H), 2.48 s (1H, OH), 7.19–7.17 m (2H, 6′-H, 7′-H), 7.55–7.54 m (1H, 3′-H), 7.60–7.57 m (2H, 5′-H, 8′-H), 7.66–7.64 m (1H, 4′-H), 8.10 s (1H, 1′-H). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 33.4 ($C^1$), 69.1 ($C^2$), 73.2 ($C^4$), 87.9 ($C^3$), 133.6–123.9 (9C, $C_{arom}$), 143.2 ($C^{2'}$). Found, %: C 85.60; H 6.19. $C_{14}H_{12}O$. Calculated, %: C 85.68; H 6.16.

**2-(Pyridin-4-yl)but-3-yn-2-ol (IIe).** Yield 18.08 g (80%), colorless crystals, mp 181–182°C. IR spectrum, ν, cm$^{-1}$: 3232, 3086, 2976, 2924, 2821, 2112, 1695, 1605, 1479, 1434, 1368, 1229, 1163, 1084, 1007, 942,

821, 709, 615, 587. $^1$H NMR spectrum (acetone-$d_6$), δ, ppm: 1.69 s (3H, $CH_3$), 3.14 s (1H, 4-H), 5.45 s (1H, OH), 7.57 d (2H, 3′-H, 5′-H, $^3J$ = 5.6 Hz), 8.54 d (2H, 2′-H, 6′-H, $^3J$ = 5.6 Hz). $^{13}$C NMR spectrum (acetone-$d_6$), $\delta_C$, ppm: 33.3 ($C^1$), 67.7 ($C^2$), 75.4 ($C^4$), 88.0 ($C^3$), 120.5 ($C^{3'}$, $C^{5'}$), 150.1 ($C^{2'}$, $C^{6'}$), 155.4 ($C^{4'}$). Found, %: C 73.91; H 5.61; N 9.61. $C_9H_9NO$. Calculated, %: C 73.45; H 6.16; N 9.52.

**2-(Furan-2-yl)but-3-yn-2-ol (IIf).** Yield 13.38 g (64%), yellow oily substance. IR spectrum, ν, cm$^{-1}$: 3541, 3402, 3295, 3125, 2994, 2938, 1571, 1502, 1468, 1396, 1362, 1292, 1243, 1227, 1160, 1099, 1011, 928, 884, 849, 816, 742, 656, 598. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.80 m (3H, $CH_3$), 2.58 s (1H, 4-H), 3.54 s (1H, OH), 6.28–6.27 m (1H, 4′-H), 6.37–6.35 m (1H, 3′-H), 7.34–7.33 m (1H, 5′-H). $^{13}$C NMR spectrum ($CDCl_3$), $\delta_C$, ppm: 28.8 ($C^1$), 64.7 ($C^2$), 72.3 ($C^4$), 85.5 ($C^3$), 106.0 ($C^{3'}$), 110.5 ($C^{4'}$), 142.5 ($C^{5'}$), 156.0 ($C^{2'}$). Found, %: C 70.45; H 5.81. $C_8H_8O_2$. Calculated, %: C 70.57; H 5.92.

**2-(Thiophen-2-yl)but-3-yn-2-ol (IIg).** Yield 17.53 g (75%), yellow oily substance. IR spectrum, ν, cm$^{-1}$: 3400, 3292, 2987, 2932, 1652, 1517, 1414, 1366, 1281, 1236, 1136, 1086, 1073, 1020, 972, 861, 841, 705, 659. $^1$H NMR spectrum ($C_6D_6$), δ, ppm: 1.86 m (3H, $CH_3$), 2.27 s (1H, 4-H), 2.33 s (1H, OH), 6.76–6.75 m (1H, 3′-H), 6.96–6.95 m (1H, 4′-H), 7.15–7.14 m (1H, 5′-H). $^{13}$C NMR spectrum ($C_6D_6$), $\delta_C$, ppm: 33.2 ($C^1$), 67.1 ($C^2$), 72.6 ($C^4$), 86.7 ($C^3$), 124.2 ($C^{3'}$), 125.2 ($C^{4'}$), 126.7 ($C^{5'}$), 150.0 ($C^{2'}$). Found, %: C 63.38; H 5.22; S 20.94. $C_8H_8OS$. Calculated, %: C 63.13; H 5.30; S 21.07.

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