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Efficient Methods of Synthesis of Unsaturated Alcohols and Ketones by Allylation of Favorsky Reaction Products under Phase Transfer Conditions

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Abstract—Allylation of the Favorsky reaction products with allyl halides under phase-transfer catalysis in the system CuI–K_2CO_3–Na_2SO_3–BTEAC–H_2O–C_6H_6 afforded the corresponding allylpropargyl alcohols in high yields (87–96%). The procedure is practical and scalable (more than 50 g of the target product can be prepared in a single run) and is characterized by high selectivity. Oxidation of secondary allylpropargyl alcohols with manganese dioxide in anhydrous acetonitrile at room temperature gave 75–81% of allylacetylenic ketones.

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Acetylene and its derivatives, in particular Favorsky reaction products, are important starting compounds in organic synthesis. Methods of synthesis of many practically valuable compounds are based on the use of Favorsky reaction products [1]. The results of studies on the Favorsky reaction and development of procedures for the preparation of propargyl alcohols containing various functional substituents have been reported in [1–6].

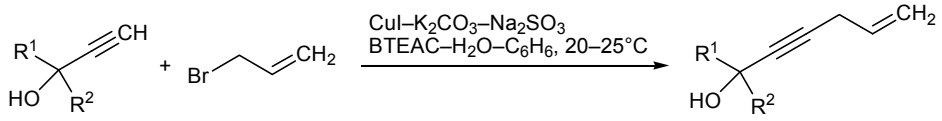
Allylacetylenes possessing both double and triple carbon–carbon bonds in their molecules could be promising intermediate products in organic synthesis; however, their chemical properties have been studied insufficiently [7–14]. Allylacetylenes were used in syntheses of natural compounds, including terpenes [11].

Allylation of acetylenes in the presence of copper(I) salts was described in [9–19]. We previously developed convenient procedures for the synthesis of pent-1-en-4-yne (allylacetylene, yield >80%) and octa-1,7-dien-4-yne (diallylacetylene) in 72% yield by cross-coupling of acetylene with allyl halides in aprotic solvents (DMF, DMSO, HMPA) under atmospheric pressure in the presence of a copper salt, base, and reducing agent [16, 17]. Hept-6-ene-1,3-diyne and deca-1,9-diene-4,6-diynes were obtained in 85–90% yield by allylation of diacetylene with allyl halides [18, 19].

Allylacetylenes containing a hydroxy or carbonyl functionality can be synthesized by allylation of propargyl alcohols obtained by the Favorsky reaction. Many propargyl alcohols are commercially available and are produced in sufficient amounts by reaction of acetylene with ketones and aldehydes [1–6].

Development of convenient and efficient procedures for the synthesis of unsaturated alcohols and ketones via allylation of Favorsky reaction products under phase-transfer catalysis is a topical problem. By reacting propargyl alcohols **1**–**5** with allyl halides at

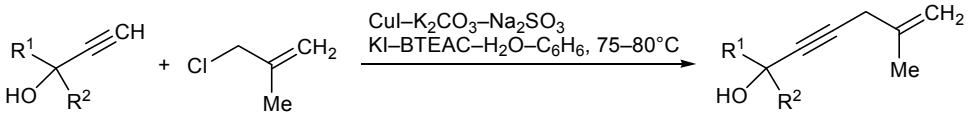
Scheme 1.



1–5 **6–10**

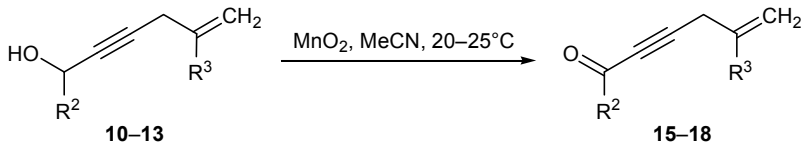
1, **6**, $R^1 = R^2$ = Me; **2**, **7**, $R^1R^2 = (CH_2)_5$; **3**, **8**, R^1 = H, R^2 = Pr; **4**, **9**, R^1 = H, R^2 = *i*-Pr; **5**, **10**, R^1 = H, R^2 = Ph.

Scheme 2.



3, **11**, R^1 = H, R^2 = Pr; **4**, **12**, R^1 = H, R^2 = *i*-Pr; **5**, **13**, R^1 = H, R^2 = Ph; **1**, **14**, R^1 = R^2 = Me.

Scheme 3.



10, **15**, R^3 = H, R^2 = Ph; **11**, **16**, R^3 = Me, R^2 = Pr; **12**, **17**, R^3 = Me, R^2 = *i*-Pr; **13**, **18**, R^3 = Me, R^2 = Ph.

room temperature under phase-transfer conditions in the presence of a base (K_2CO_3, alkali metal hydroxide), reducing agent ($Na_2S_2O_5$, Na_2SO_3, hydrazine hydrate), and catalytic amount of copper(I) halide (CuI, CuBr, CuCl) we obtained with high yields (87–96%) compounds **6**–**10** (Scheme 1); no inert atmosphere was necessary. The procedure ensured high selectivity, and allylpropargylic alcohols **6**–**10** isolated by extraction from the reaction mixture had a purity of >96% without additional purification. Allyl bromide was found to be more effective allylating agent than allyl chloride.

Relatively small amounts of allylpropargylic alcohols were obtained by the known methods, and the yields were lower [12–15]. The procedure developed by us is experimentally simple, practically feasible, efficient, and scalable; more than 50 g of the target product can be obtained in a single run at room temperature from 0.5–1 mol of starting compounds.

When 3-chloro-2-methylprop-1-ene was used instead of allyl bromide, the yield of the allylation products decreased to 20–40%. However, raising the temperature to 75–80°C and adding a catalytic amount of potassium iodide allowed us to improve the yield of **11**–**14** to 85–94% (Scheme 2).

Allylacetylenic ketones can be synthesized by either oxidation of the obtained allylpropargyl alcohols or allylation of the corresponding ethynyl ketones. The first approach is more efficient. By oxidation of **10**–**13** with manganese dioxide in anhydrous acetonitrile at room temperature we synthesized allylacetylenic ketones **15**–**18** in 75–81% yield (Scheme 3). Unsaturated alcohols and ketones **6**–**18** are promising as intermediate products in organic synthesis. Development of efficient methods for the preparation of these compounds makes them accessible and provides the possibility of detailed study of their chemical properties and scope of application, in particular in addition and cyclization reactions with chalcogen-containing reagents [20].

EXPERIMENTAL

The NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker DPX-400 spectrometer at 400.13 (^{1}H) and 100.61 MHz (^{13}C) using hexamethyldisiloxane as reference. The elemental analyses were obtained on a Thermo Flash EA1112 analyzer. Distilled anhydrous acetonitrile was used as solvent in the oxidation reactions. Compounds **6** and **14** were described previously [13–15], but their ^{13}C NMR spectra were not given.

Compounds 6–10 (*general procedure***).** A mixture of 2.76 g (20 mmol) of K_2CO_3, 1 g (7.9 mmol) of Na_2SO_3, 0.5 g (2.6 mmol) of CuI, 0.2 g (0.8 mmol) of BTEAC, and 15 mL of water was stirred for 5 min, a solution of 20 mmol of alcohol **1**–**5** and 3 g (24.8 mmol) of allyl bromide in 10 mL of benzene were added, and the mixture was vigorously stirred for 16 h at room temperature. A solution of 4 g of ammonium chloride in 20 mL of water was added, the organic layer was separated, and the aqueous phase was extracted with benzene (2×10 mL). The extracts were combined with the organic phase and dried over $CaCl_2$, the solvent was removed on a rotary evaporator, and the residue was dried under reduced pressure.

2-Methylhept-6-en-3-yn-2-ol (6). Yield 96%. ^{1}H NMR spectrum, δ, ppm: 1.50 s (6H, CH_3), 2.80 s (OH), 2.95 d (2H, =CHC**H**$_2$, ^3J = 6 Hz), 5.09 d (1H,

=CH_2, ^3J = 10 Hz), 5.30 d (1H, =CH_2, ^3J = 16.9 Hz), 5.79 m (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 22.63 (=CH**C**H_2), 31.42 (CH_3), 64.93 (COH), 78.55 (≡C), 87.56 (≡C), 115.74 (CH_2=), 132.30 (=CH).

Enlarged synthesis of compound 6. A mixture of 69 g (0.5 mol) of K_2CO_3, 25.2 g (0.2 mmol) of Na_2SO_3, 11.4 g (60 mmol) of CuI, 4.56 g (20 mmol) of benzyl(triethyl)ammonium chloride, and 350 mL of water was stirred for 30 min, a solution of 42 g (0.5 mol) of alcohol **1** and 66.6 g (0.55 mol) of allyl bromide in 250 mL of benzene was added, and the mixture was vigorously stirred for 68 h at room temperature. A solution of 100 g of ammonium chloride in 500 mL of water was then added, the organic phase was separated, and the aqueous phase was extracted with benzene (3×100 mL). The extracts were combined with the organic phase and dried over $CaCl_2$, the solvent was removed on a rotary evaporator, and the residue was dried under reduced pressure. Yield 50.3 g (81%).

1-(Pent-4-en-1-yn-1-yl)cyclohexan-1-ol (7). Yield 87%. ^{1}H NMR spectrum, δ, ppm: 1.12–1.22 (2H, CH_2), 1.40–1.52 (4H, CH_2), 1.53–1.62 (2H, CH_2), 1.73–1.83 (2H, CH_2), 2.64 s (OH), 2.89 d (2H, =CHC**H**$_2$, ^3J = 6.1 Hz), 5.06 d (1H, =CH_2, ^3J = 9.9 Hz), 5.25 d (1H, =CH_2, ^3J = 16.9 Hz), 5.75 m (=CH). ^{13}C NMR spectrum, δ_C, ppm: 22.81 (=CH**C**H_2), 23.14 (CH_2), 24.95 (CH_2), 39.91 (CH_2), 68.44 (COH), 80.52 (≡C), 87.69 (≡C), 115.68 (=CH_2), 132.39 (=CH). Found, %: C 80.14; H 9.63. $C_{11}H_{16}O$. Calculated, %: C 80.44; H 9.82.

Non-8-en-5-yn-4-ol (8). Yield 90%. ^{1}H NMR spectrum, δ, ppm: 0.91 t (3H, CH_3), 1.46 m (2H, CH_2), 1.65 m (2H, CH_2), 2.49 s (1H, OH), 2.96 d (2H, =CH**C**H_2, ^3J = 6 Hz), 4.36 m (1H, OCH), 5.08 d (1H, =CH_2, ^3J = 10 Hz), 5.28 d (1H, =CH_2, ^3J = 17 Hz), 5.77 m (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 13.55 (CH_3), 18.28 (CH_3), 22.79 (=CH**C**H_2), 39.94 (CH_2), 62.11 (CHOH), 81.37 (≡C), 83.73 (≡C), 115.87 (CH_2=), 132.21 (CH=). Found, %: C 78.51; H 10.39. $C_9H_{14}O$. Calculated, %: C 78.21; H 10.21.

2-Methyloct-7-en-4-yn-3-ol (9). Yield 91%. ^{1}H NMR spectrum, δ, ppm: 0.91 d (6H, CH_3), 1.78 m (1H, C**H**CH_3), 2.92 d (2H, =CHC**H**$_2$, ^3J = 6 Hz), 3.01 s (1H, OH), 4.08 m (1H, OCH), 5.02 d (1H, =CH_2, ^3J = 10 Hz), 5.25 d (1H, =CH_2, J = 17 Hz), 5.73 m (1H, =CH). ^{13}C NMR spectrum, δ_C, ppm: 17.49 (CH_3), 18.19 (CH_3), 22.99 (=CH**C**H_2), 34.59 (**C**HCH_3), 67.64 (CHOH), 81.87 (≡C), 82.66 (≡C), 116.01 (CH_2=), 132.55 (CH=). Found, %: C 78.03; H 10.02. $C_9H_{14}O$. Calculated, %: C 78.21; H 10.21.

1-Phenylhex-5-en-2-yn-1-ol (10). Yield 87%. ^{1}H NMR spectrum, δ, ppm: 2.86 s (1H, OH), 3.07 d (2H, =CHC**H**$_2$, ^3J = 6 Hz), 5.16 (1H, =CH_2, ^3J = 10 Hz), 5.18 (1H, =CH_2, ^3J = 17 Hz), 5.49 m (1H, OCH), 5.86 m (1H, =CH), 7.32–7.41 m (3H, Ph), 7.56–7.57 (2H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 22.84 (=CH**C**H_2), 64.05 (CHOH), 82.79 (≡C), 82.87 (≡C), 116.26 (CH_2=), 126.17 (C_{arom}), 127.88 (C_{arom}), 127.49 (C_{arom}), 131.64 (CH=), 140.99 (C_{arom}). Found, %: C 83.43; H 6.85. $C_{12}H_{12}O$. Calculated, %: C 83.69; H 7.02.

Compounds 11–14 (*general procedure*). A mixture of 2.76 g (20 mmol) of K_2CO_3, 1 g (7.9 mmol) of Na_2SO_3, 0.5 g (2.6 mmol) of CuI, 0.3 g (1.8 mmol) of KI, 0.2 g (0.8 mmol) of BTEAC, and 15 mL of water was stirred for 5 min. A solution of 20 mmol of alcohol **1**–**5** and 2.3 g (25 mmol) of 3-chloro-2-methylprop-1-ene in 10 mL of benzene was added, and the mixture was heated for 6 h at 75–80°C under stirring. After cooling, the mixture was treated with a solution of 4 g of NH_4Cl in 20 mL of water, the organic phase was separated, and the aqueous phase was extracted with benzene (2×10 mL). The extracts were combined with the organic phase and dried over $CaCl_2$, and the solvent was removed on a rotary evaporator.

8-Methylnon-8-en-5-yn-4-ol (11). Yield 85%. ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3), 1.39 m (2H, CH_2), 1.60 m (2H, CH_2), 1.70 s (3H, CH_3), 2.84 s (2H, =CCH_2), 2.90 s (OH), 4.28 m (1H, OCH), 4.74 s and 4.90 s (1H each, =CH_2). ^{13}C NMR spectrum, δ_C, ppm: 13.38 (CH_3), 18.28 (CH_3), 21.88 (CH_3), 27.46 (=C**C**H_2), 40.01 (HOCH**C**H_2), 62.31 (CHOH), 82.07 (≡C), 83.88 (≡C), 111.73 (CH_2=), 140.48 (=C). Found, %: C 79.12; H 10.73. $C_{10}H_{16}O$. Calculated, %: C 78.90; H 10.59.

2,7-Dimethyloct-7-en-4-yn-3-ol (12). Yield 90%. ^{1}H NMR spectrum, δ, ppm: 0.90 t (6H, CH_3), 1.69 s (3H, CH_3), 1.77 m (1H, C**H**CH_3), 2.83 s (2H, =CCH_2), 2.95 s (OH), 4.09 m (1H, OCH), 4.72 s (1H, =CH_2), 4.91 s (1H, =CH_2). ^{13}C NMR spectrum, δ_C, ppm: 17.32 (CH_3), 18.14 (CH_3), 21.85 (CH_3), 27.36 (=C**C**H_2), 34.68 (**C**HCH_3), 67.74 (CHOH), 82.35 (≡C), 83.04 (≡C), 111.55 (=CH_2), 140.43 (=C). Found, %: C 79.16; H 10.47. $C_{10}H_{16}O$. Calculated, %: C 78.90; H 10.59.

5-Methyl-1-phenylhex-5-en-2-yn-1-ol (13). Yield 94%. ^{1}H NMR spectrum, δ, ppm: 1.83 s (3H, CH_3), 3.07 s (2H, =CCH_2), 3.42 s (1H, OH), 4.90 m and

5.08 m (1H, CH_2=), 5.42 s (1H, C**H**OH), 7.36–7.42 m (3H, Ph), 7.57–7.61 m (2H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 22.19 (CH_3), 27.63 (=C**C**H_2), 64.66 (CHOH), 83.91 (≡C), 84.33 (≡C), 112.05 (=CH_2), 126.75 (C_{arom}), 128.64 (C_{arom}), 129.06 (C_{arom}), 140.35 (=C), 141.30 (C_{arom}). Found, %: C 83.58; H 7.39. $C_{13}H_{14}O$. Calculated, %: C 83.83; H 7.58.

2,6-Dimethylhept-6-en-3-yn-2-ol (14). Yield 92%. ^{1}H NMR spectrum, δ, ppm: 1.47 s (6H, CH_3), 1.73 s (3H, CH_3), 2.67 s (1H, OH), 2.85 s (2H, =CCH_2), 4.78 s (1H, =CH_2), 4.95 s (1H, =CH_2). ^{13}C NMR spectrum, δ_C, ppm: 21.96 (CH_3), 27.27 (=C**C**H_2), 31.60 (CH_3), 65.12 (CHOH), 79.25 (≡C), 87.70 (≡C), 111.55 (=CH_2), 140.40 (=C).

Compounds 15–18 (*general procedure***).** A mixture of 5 mmol of compound **10**–**13**, 2 g (23 mmol) of MnO_2, and 20 mL of acetonitrile was vigorously stirred for 16 h at room temperature. The mixture was filtered, and the precipitate was washed with acetonitrile on a filter. The solvent was distilled off from the filtrate, and the residue was purified by silica gel chromatography using hexane–chloroform (8 : 1) as eluent.

1-Phenylhex-5-en-2-yn-1-one (15). Yield 80%. ^{1}H NMR spectrum, δ, ppm: 3.25 d (2H, =CHC**H**$_2$, ^3J = 6 Hz), 5.21 d (1H, =CH_2, ^3J = 10 Hz), 5.40 d (1H, ^3J = 17 Hz), 5.87 m (1H, =CH), 7.42–7.50 m (2H, Ph), 7.54–7.60 m (1H, Ph), 8.10–8.16 m (2H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 23.41 (=CH**C**H_2), 81.32 (≡C), 92.51 (≡C), 113.70 (=CH_2), 128.51 (C_{arom}), 129.53 (C_{arom}), 130.09 (C_{arom}), 134.04 (=CH), 136.83 (C_{arom}), 177.95 (C=O). Found, %: C 84.93; H 6.09. $C_{12}H_{10}O$. Calculated, %: C 84.68; H 5.92.

8-Methylnon-8-en-5-yn-4-one (16). Yield 76%. ^{1}H NMR spectrum, δ, ppm: 0.86 t (3H, CH_3), 1.61 m (2H, CH_2), 1.81 s (3H, CH_3), 2.45 t (CH_2C=O), 3.00 s (2H, =CCH_2), 4.81 s and 4.91 s (1H each, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 13.30 (CH_3), 17.43 (CH_2), 21.87 (CH_3), 27.37 (=C**C**H_2), 47.23 (**C**H_2C=O), 82.39 (≡C), 90.63 (≡C), 112.78 (=CH_2), 138.19 (=C), 188.26 (C=O). Found, %: C 80.15; H 9.57. $C_{10}H_{14}O$. Calculated, %: C 79.96; H 9.39.

2,7-Dimethyloct-7-en-4-yn-3-one (17). Yield 75%. ^{1}H NMR spectrum, δ, ppm: 1.06 d (6H, CH_3), 1.69 s (3H, CH_3), 2.51 m (1H, CHC=O), 2.97 s (2H, =CCH_2), 4.77 s and 4.88 s (1H each, CH_2=). ^{13}C NMR spectrum, δ_C, ppm: 18.02 (CH_3), 22.64 (CH_3), 27.69 (=C**C**H_2), 43.13 (**C**HC=O), 81.61 (≡C), 91.78 (≡C), 113.04 (=CH_2), 138.52 (=C), 192.46 (C=O). Found, %: C 79.81; H 9.23. $C_{10}H_{14}O$. Calculated, %: C 79.96; H 9.39.

5-Methyl-1-phenylhex-5-en-2-yn-1-one (18). Yield 81%. ^{1}H NMR spectrum, δ, ppm: 1.85 s (3H, CH_3), 3.08 s (2H, =CCH_2), 4.80 s and 4.93 s (1H each, =CH_2), 7.36–7.43 m (2H, Ph), 7.57–7.61 m (1H, Ph), 8.13–8.19 m (2H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 22.83 (CH_3), 28.40 (=C**C**H_2), 81.70 (≡C), 93.43 (≡C), 113.76 (=CH_2), 129.71 (C_{arom}), 130.33 (C_{arom}), 134.78 (=CH), 136.92 (C_{arom}), 138.52 (C_{arom}), 178.25 (C=O). Found, %: C 84.58; H 6.37. $C_{13}H_{12}O$. Calculated, %: C 84.75; H 6.57.

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