Alkoxide-Catalyzed Addition of Terminal Alkynes to Ketones

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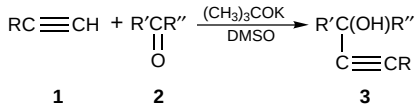
The coupling of a terminal alkyne (**1**) to a ketone to generate a tertiary alkynol (**3**) is a well-established alkylation methodology in organic synthesis. This process is usually initiated by conversion of the alkyne to the corresponding acetylide anion ($RC{\equiv}C^-$) using 1 equiv of an air-sensitive, strong base such as methylmagnesium bromide,[1] butyllithium,[2] or sodium amide[3] prior to addition of the ketone. The notion that 1 equiv of a strong base is required for this alkynylation process is not surprising in view of the known acidities[4] of a terminal alkyne and other weak acids whose conjugate bases one might utilize to generate an acetylide anion: R_3COH ($pK_a = 17$); $RCOCH_2R$ (an enolizable ketone, $pK_a = 19-20$); $RC{\equiv}CH$ ($pK_a = 25$); NH_3 ($pK_a = 38$); and CH_3CH_2H ($pK_a = 50$). These data suggest that, in contrast to strong bases such as ethylmagnesium bromide or sodium amide, an alkoxide derived from a tertiary alcohol should be too weakly basic to convert (appreciably) a terminal alkyne to an acetylide anion. There are several patents[5] that relate to the use of potassium hydroxide, which is comparable in basicity to an alkoxide, as a catalyst in the reaction of gaseous acetylene with carbonyl compounds in liquid ammonia—a process referred to as the Favorskii reaction. However, subsequent research[6] demonstrated that the Favorskii conditions do not involve an acid−base reaction to generate an alkali metal acetylide, but instead the reaction proceeds via formation of an acetylene−alkali hydroxide complex.

It occurred to us that a more economical and conceptually simple methodology should be feasible to effect this alkynylation process, after examining the following known[7] equilibrium acidities measured in dimethyl sulfoxide (DMSO): cyclohexanone ($pK_a = 26.4$); phenylacetylene ($pK_a = 28.7$); and *tert*-butyl alcohol ($pK_a = 32.2$). Such data suggest that *tert*-butoxide should be capable of converting a terminal alkyne to the corresponding acetylide anion in DMSO. Moreover, since the initial product when the alkynylation occurs is a tertiary alkoxide, the process should be catalytic with respect to the base. Although we were concerned that a competitive process (i.e., an aldol condensation) was possible for enolizable ketones, such a reaction is known to be reversible and therefore perhaps could be minimized.[8]

Scheme 1



1 **2** **3**

	R	2
a	$(CH_2)_5CH_3$	cyclohexanone
b	C_6H_5	3-pentanone
c	$HOC(CH_3)_2$	cyclohexanone
d	CH_2OTHP	cyclohexanone
e	CH_2OH	cyclohexanone
f	$CH_2CH(OH)CH_3$	2-butanone
g	$CH_2CH(ONa)CH_3$	2-butanone

In order to test our proposed methodology, a catalytic amount (10−20 mol %) of potassium *tert*-butoxide was added to a DMSO solution containing equimolar amounts of cyclohexanone and 1-octyne (Scheme 1). After several hours at room temperature, we were pleased to obtain the corresponding tertiary alkynol **3a** in 80−90% distilled yield. Remarkably, the process also occurred, albeit at a slower rate, in nonpolar solvents such as benzene.[9] To assess further the scope of this methodology, several representative alkynes and ketones were subjected to the standard reaction conditions (i.e., catalytic potassium *tert*-butoxide in DMSO at room temperature). As can be seen from the data in the Experimental Section, distilled yields of tertiary alkynols were generally 70−90% and no significant side reactions were observed. Although the process was successful even in the presence of an unblocked tertiary alcohol functionality (**1c** → **3c**), we found it essential to convert a reactant alkynol possessing a secondary alcohol functionality (**1f**) *in situ* to the corresponding alkoxide salt (**1g**)[10] prior to initiating the alkynylation.

Our results demonstrate that a variety of tertiary alkynols can indeed be prepared via a catalytic process that avoids the use of air-sensitive bases such as butyllithium. This process may prove to be especially useful in large-scale alkynylation reactions.

Experimental Section

General Methods. Methyl sulfoxide (DMSO, HPLC grade) was purchased from Aldrich Chemical Co. and used without further purification. Unless specified otherwise, all organic reagents were purchased from Aldrich Chemical Co. All reactions were protected from atmospheric moisture and CO_2 by connecting the reaction flask to an apparatus similar to that

(1) Viehe, H. G.; Reinstein, M. *Chem. Ber.* **1962**, *95*, 2557.
(2) Eaton, P. E.; Srikrishna, A.; Uggeri, F. *J. Org. Chem.* **1984**, *49*, 1728.
(3) Saunders, J. H. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 416.
(4) March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; John Wiley & Sons: New York, 1992; Table 8.1, pp 250−2.
(5) These patents are cited by Tedeschi, R. J.; Casey, A. W.; Clark, G. S., Jr.; Huckel, R. W.; Kindley, L. M.; Russell, J. P. *J. Org. Chem.* **1963**, *28*, 1740.
(6) Tedeschi, R. J. *J. Org. Chem.* **1965**, *30*, 3045. For a more extensive discussion of the ethynylation of carbonyl compounds, see: Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: Amsterdam, 1988; pp 79−96.
(7) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(8) Only in reactions involving a methyl ketone was a competitive aldol condensation an observable side reaction. Even then, the latter could be prevented by slow addition of the methyl ketone to the DMSO solution containing the terminal alkyne and alkoxide catalyst. Attempts to utilize an enolizable aldehyde (e.g., propionaldehyde and isobutyraldehyde) in this process, however, led to a complex mixture of products.
(9) Use of other aprotic solvents in lieu of DMSO is feasible, although the rate at which alkynylation occurs decreases in less polar solvents. For example, use of tetrahydrofuran as the solvent in lieu of DMSO afforded alkynol **3a** in approximately 50% yield after a reaction time of 20 h at room temperature. The rest of the product mixture consisted of unreacted starting materials. A similar experiment using benzene as the solvent afforded alkynol **3a** in 35% yield after a reaction time of 20 h.
(10) We observed that the alkoxide **1g** derived from 4-pentyn-2-ol isomerized rapidly to 3,4-pentadien-2-ol (characterized by an IR absorption at 1960 cm^{-1}) when treated with $KOC(CH_3)_3$ in DMSO at room temperature. Since the latter allenyl alcohol was the major component in the reaction mixture after 2 h, its formation appears to be reversible. In none of the systems examined was the tertiary alkynol **3** contaminated with any allenic impurities.

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described by Johnson and Schneider.[11] Products were recovered from the organic extracts after drying over anhydrous sodium sulfate and removal of the solvent with a rotary evaporator under reduced pressure. Unless indicated otherwise, IR analysis of the crude alkynol product confirmed the absence of any unreacted starting ketone. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. The physical and spectral properties of all alkynols were minimally consistent with the data in the literature.

1-[3-[(Tetrahydropyran-2-yl)oxy]-1-propynyl]cyclohexanol (3d). To a solution of 704 mg (5.02 mmol) of 3-[(tetrahydropyran-2-yl)oxy]propyne (**1d**),[12] prepared from 2-propyn-1-ol using a procedure described by Grieco and co-workers,[13] and 0.50 mL (4.82 mmol) of cyclohexanone (**2d**) in 3.00 mL of DMSO was added 112 mg (1.0 mmol) of potassium *tert*-butoxide.[14] This mixture was subsequently stirred, while being protected[11] from atmospheric moisture and CO_2 at room temperature for 15 h. The mixture was then diluted with 25 mL of 10% (w/v) aqueous sodium chloride, and the product was isolated by extraction with 30 mL of 1:1 (v/v) hexane:ether. The organic layer was washed in succession with 10% (w/v) aqueous sodium chloride (3 × 25 mL) and saturated brine (1 × 25 mL). The product was then isolated from the organic extract in the usual manner and purified by evaporative distillation: bp 120−138 °C (bath temperature, 0.25 Torr) [lit.[15] bp 124−127 °C at 0.30 Torr], affording 1.047 g (91%)[16] of alkynol **3d** as a viscous oil, shown by ^{1}H and ^{13}C NMR to be essentially free of impurities: IR ν_{max} (film) 3420 (OH), 1200, 1182, 1130, 1117, 1075, 1055, 1025, 965, 945, 900, 870, 815 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 [t, J = 3.0 Hz, OCHO], 4.31 [s, $CH_2C{\equiv}C$], 3.84 [t, J = 9.6 Hz, 1H], 3.56 (m, 1H), 3.12 (s, OH), 1.52−1.92 (m, 14H), 1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 96.205, 89.757, 79.463, 68.114, 61.628, 54.065, 39.607, 30.018, 25.163, 24.996, 23.032, 18.753.

3-Ethyl-1-phenyl-1-pentyn-3-ol (3b). Reaction of equivalent amounts of phenylacetylene (**1b**) and 3-pentanone (**2b**) in the presence of a catalytic amount of potassium *tert*-butoxide as described in the procedure for the preparation of alkynol **3d** afforded adduct **3b** in 70% distilled yield: bp 97−112 °C (bath temperature, 0.25 Torr) [lit.[17] bp 138−142 °C at 12 Torr]; IR ν_{max} (film) 3390 (OH), 1597, 1485, 1140, 955, 753, 688 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 3.6 Hz, 2 ortho H's), 7.29 (m, 3H), 2.32 (s, OH), 1.778 (2H, q, J = 7.2 Hz, one of the diastereotopic methylene protons), 1.768 (2H, q, J = 7.2 Hz), 1.11 (t, J = 7.2 Hz, 2 × CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.522, 128.068, 128.000, 122.791, 91.692, 84.387, 72.508, 34.475, 8.735.

1-(1-Octynyl)cyclohexanol (3a). Reaction of equivalent amounts of 1-octyne (**1a**) and cyclohexanone (**2a**) with a catalytic amount of potassium *tert*-butoxide[18] in DMSO[9] as described in the procedure for the preparation of **3d** afforded alkynol **3a** in 84% distilled yield: bp 110−122 °C (bath temperature, 0.25 Torr) [lit.[1] bp 97 °C at 0.015 Torr]; IR ν_{max} (film) 3370 (OH), 1060, 958, 898 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, OH), 2.20 (t, J = 7.0 Hz, $CH_2C{\equiv}C$), 1.86 (m, 2H), 1.67 (m, 2H), 1.52 (m, 7H), 1.39 (m, 2H), 1.29 (m, 5H), 0.89 (t, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.586, 83.888, 68.633, 40.186, 31.196, 28.655, 28.374, 25.188, 23.360, 22.435, 18.536, 13.885.

1-(3-Hydroxy-3-methyl-1-butynyl)cyclohexanol (3c). Reaction of equivalent amounts of 2-methyl-3-butyn-2-ol (**1c**) and cyclohexanone (**2c**) in the presence of a catalytic amount of potassium *tert*-butoxide as described in the procedure[19] for the preparation of alkynol **3d** afforded alkynediol **3c** in 53% yield,[20] the mp and IR and proton NMR spectral properties of which were consistent with those previously reported:[21] ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.002, 85.383, 68.254, 64.712, 39.633, 31.319, 25.038, 23.399.

6-Methyl-4-octyne-2,6-diol (3f). A solution of 0.50 mL (5.3 mmol) of 4-pentyn-2-ol (**1f**) in 3.00 mL of DMSO was added dropwise slowly over 10 min to 5.3 mmol of sodium hydride (60% dispersion in mineral oil, which was removed prior to the reaction by washing with hexane), protected from atmospheric moisture[11] and maintained at a temperature of 15 °C by use of an external cold water bath. Once hydrogen evolution had ceased, 0.05 mL (0.55 mmol) of 2-butanone and 55 mg (0.49 mmol) of potassium *tert*-butoxide were added to initiate the alkynylation process.[22] This mixture was stirred at room temperature for 45 min, after which three additional portions[23] (3 × 0.05 mL) of 2-butanone were added at 45 min intervals. After addition of the last portion of 2-butanone, the reaction mixture was stirred for an additional 2 h. The mixture was then diluted with 25 mL of 10% (w/v) aqueous sodium chloride, and the product was isolated by extraction with 25 mL of 4:1 (v/v) ether:dichloromethane. The organic layer was washed in succession with 10% (w/v) aqueous sodium chloride (3 × 25 mL) and saturated brine (1 × 25 mL). The product was then isolated from the organic extract in the usual manner and purified by evaporative distillation: bp 102−120 °C (bath temperature, 0.25 Torr) [lit.[24] bp 112 °C at 2 Torr], affording 218 mg (63%)[25] of alkynediol **3f** shown by NMR analysis to be a mixture of diastereomers: IR ν_{max} (film) 3340 (OH), 1210, 1158, 1120, 1085, 988, 938, 910 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (sextet, 1H, J = 6.0 Hz), 3.50 (broad s, OH), 3.32 (broad s, OH), 2.36 (m, 2H), 1.67 (m, 2H), 1.452 and 1.445 (s, 3H), 1.26 (d, 3H, J = 6.0 Hz), 1.023 and 1.019 (t, 3H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.268, 79.911, 68.540, 66.249, 36.566, 29.245, 28.949, 22.175, 9.067; other diastereomer 86.245, 79.858, 68.540, 66.302, 36.490, 29.298, 28.934, 22.160, 9.067.

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(11) The reaction flask was connected to an apparatus similar to that described by Johnson, W. S.; Schneider, W. P. *Org. Synth.* **1950**, *30*, 18.

(12) Picard, P.; Moulines, J. *Bull. Soc. Chim. Fr.*, Part II **1974**, 2256.

(13) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.

(14) Purchased from Lancaster Synthesis, Windham, NH.

(15) Claesson, A.; Bogentoft, C. *Acta Chem. Scand.* **1972**, *26*, 2540.

(16) In an identical experiment using 2-propyn-1-ol as the alkyne in lieu of 3-[(tetrahydropyran-2-yl)oxy]propyne (**1d**), the expected adduct **3e** was obtained, but the reaction rate was too slow at room temperature (less than 30% conversion after 2 days). This result indicates that the alkynylation process requires the blocking—or conversion to the corresponding alkoxide salt—of primary alcohols, although not tertiary alcohols (*vide infra*).

(17) Papa, D.; Villani, F. J.; Ginsberg, H. F. *J. Am. Chem. Soc.* **1954**, *76*, 4446.

(18) Potassium methoxide, as well as powdered potassium hydroxide (ACS reagent, 85%), can be used as the catalyst in this alkynylation process. However, these bases were less effective than potassium *tert*-butoxide since conversion to the desired adduct **3a** was only approximately 40% after a reaction time of 10 h. Sodium alkoxide bases were even less efficient catalysts for this process. For example, replacement of $KOC(CH_3)_3$ with $NaOCH_3$ resulted in a product mixture containing only 15% of the desired tertiary alkynol **3a** after 1 day at room temperature.

(19) The following modification was made: alkynediol **3c** was extracted from the reaction mixture, after dilution with 10% aqueous NaCl, using 4:1 (v/v) ether:dichloromethane in lieu of 1:1 (v/v) hexane:ether.

(20) The moderate yield of alkynediol **3c** in this experiment may arise from the difficulty in separating **3c** from DMSO—i.e., removal of the latter with several aqueous NaCl washes undoubtedly results in partial loss of the polar diol **3c**. The unblocked tertiary alcohol moiety in 2-methyl-3-butyn-2-ol did not appreciably slow down the alkynylation process since only a minor amount (5−10%) of unreacted cyclohexanone was detected in the crude product mixture.

(21) Saimoto, H.; Hiyama, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3078.

(22) A subsequent experiment demonstrated that addition of $KOC(CH_3)_3$ is unnecessary for the success of this reaction—an indication that the alkoxide derived from 4-pentyn-2-ol can serve as the catalyst for the process. However, if $KOC(CH_3)_3$ is present as a catalyst but 4-pentyn-2-ol is *not* converted to an alkoxide derivative, the alkynylation process is very sluggish.

(23) In a similar experiment that involved the addition of 0.20 mL (2.2 mmol) of 2-butanone in one portion to the reaction mixture, aldol condensation was observed as a side reaction.

(24) Favorskaya, T. A.; Medvedeva, A. S.; Vlasov, V. M.; Chichkareva, G. G. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1967**, 2107−9.

(25) The moderate yield in this experiment may arise from the difficulty in separating the polar alkynediol **3f** from DMSO. In a similar experiment, the sodium alkoxide derivative **1g** of 4-pentyn-2-ol was coupled with a higher-molecular-weight methyl ketone (6-methyl-5-hepten-2-one) and a 93% distilled yield of the less polar C-13 alkynediol (6,10-dimethyl-9-undecen-4-yne-2,6-diol) was obtained. See: Babler, J. H. U.S. Patent 5,349,071 (Sept. 20, 1994), Example XV.