

A Convenient Synthesis of α,β -Acetylenic Ketones

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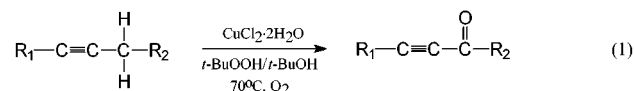
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α,β -Acetylenic ketones are extremely versatile intermediates for the preparation of various heterocyclic compounds,¹ anticancer agents,² pyrazole derivatives,³ nucleosides,⁴ sex pheromones⁵ and β -keto-1,3-dithianes⁶ as well as other compounds.⁷ Thus, considerable effort has been devoted to the preparation of conjugated acetylenic ketones based on a wide variety of synthetic approaches including the acylation of metal acetylides,⁸ Cu(I)-catalyzed cross coupling between terminal alkynes and acid chlorides,⁹ and multistep synthesis.¹⁰ Besides these methods, direct α -oxidation of alkynes to the corresponding α,β -acetylenic ketones has been attempted previously with varying success. For example, Shaw and Sherry reported the use of chromium trioxide–pyridine complex or sodium chromate in the oxidation of various alkynes.¹¹ An excess of oxidant was required, and low yields were obtained. This reaction was improved slightly

by Muzart and Piva by using *tert*-butyl hydroxide (TBHP) with catalytic amounts of CrO₃ and *p*-toluenesulfonic acid.¹² However, an excess of TBHP (up to 7 equiv) and a long reaction time were required. Oxidation of a variety of alkynes¹³ and acetylenic fatty esters¹⁴ with TBHP catalyzed by selenium dioxide has also been reported. A mixture of monoxygenated and dioxygenated acetylenic alcohols or ketones was obtained. Recently, Ishii and co-workers reported a successful catalytic aerobic oxidation of alkynes to conjugated acetylenic ketones using *N*-hydroxyphthalimide (NHPI) combined with a transition metal under mild conditions.¹⁵ For example, oxidation of 4-octyne with NHPI (10 mol %) and [Co(acac)₂] (0.5 mol %) in acetonitrile under oxygen at 50 °C for 6 h gave 85% conversion with 72% selectivity to 4-octyne-3-one. Some byproducts such as acetylenic alcohol, acetylenic diketone, and a cleaved product, butanoic acid, were also produced.

As part of a continuing effort to develop novel selective oxidation of organic compounds using inexpensive transition metal catalysts and molecular oxygen,¹⁶ herein we report a copper(II) chloride-catalyzed oxidation of alkynes (RC≡CCH₂R') with oxygen and *tert*-butyl hydroperoxide in *tert*-butyl alcohol to the corresponding α,β -acetylenic ketones, RC≡CCOR', under mild conditions (eq 1). The



R₁ = H, aliphatic or aromatic group

R₂ = aliphatic group

method gives both high conversion and selectivity in the formation of the α,β -acetylenic ketone. This is facilitated since the intermediate acetylenic alcohol, RC≡CCH(OH)R', a frequent side product of other syntheses, is smoothly converted to the ketone under the reaction conditions and the product ketone is deactivated from further reaction. The reaction is an example of highly regio- and chemoselective C–H bond activation.

Since metal-catalyzed decomposition of hydroperoxides depends on the nature of metal complexes, a wide range of TBHP autoxidation conditions using different metal catalysts including Co(acac)₃, CoBr₂, CoCl₂, Co(OAc)₂·4H₂O, CrCl₃·6H₂O, CuCl₂·2H₂O, FeCl₂·*n*H₂O, and MnCl₂·6H₂O were examined, using 4-octyne as a model substrate. Table 1 shows that all of the metal catalysts gave high conversions ranging from 81 to 96%, with cobalt and copper catalysts leading to the highest selectivity for the 4-octyn-3-one. Use of iron and manganese chlorides gave a higher yield of the alcohol, 4-octyn-3-ol. These findings suggest that the metal catalysts used have a similar ability to decompose the TBHP into the radical species

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Table 1. Effect of Metal Catalysts on the Oxidation of 4-Octyne with TBHP^a

Metal Catalyst	Conv. ^b (%)	Product Distribution ^c (%)	
		$\text{C}_3\text{H}_7\text{C}=\text{C}(\text{O})\text{C}_2\text{H}_5$	$\text{C}_3\text{H}_7\text{C}=\text{C}(\text{OH})\text{C}_2\text{H}_5$
Without catalyst	56	17	80
Co(acac) ₃	89	96	2
CoBr ₂	89	92	4
CoCl ₂	88	96	2
CoCl ₂ ·6H ₂ O	91	97	1
Co(OAc) ₂ ·4H ₂ O	89	92	5
CrCl ₃ ·6H ₂ O	81	95	2
CuCl ₂ ·2H ₂ O	91	97	1
FeCl ₂ ·nH ₂ O	83	72	23
MnCl ₂ ·6H ₂ O	96	68	31

^a Metal catalyst (0.18 mmol), 4-octyne (4.5 mmol), and *t*-BuOOH (3.15 mmol); molar ratio = 1:25:17.5. The reaction was carried out at 70 °C under O₂ for 24 h. ^b Conversion was determined on the basis of the internal standard, *tert*-butylbenzene. ^c Product distributions were determined by GC. Small amounts of unidentified products were also observed.

that initiate the oxidation of 4-octyne. However, they vary in converting the alcohol intermediate to the conjugated acetylenic ketone.

The effect of copper(II) chloride concentration was also investigated, as shown in Table 2. It was found that varying the molar ratio of CuCl₂·2H₂O and 4-octyne over the range of 1:10 to 1:200 had little influence on the conversion, but decreasing the copper(II) chloride concentration resulted in lower selectivity of the formation of 4-octyn-3-one. Interestingly, the control reaction using no metal catalyst also gave a significant amount of 4-octyn-3-ol in spite of its low conversion. These results clearly indicate that the metal catalyst not only promotes the decomposition of TBHP but also plays a key role in converting the acetylenic alcohol intermediate to the α,β -acetylenic ketone.

Molar ratios of 4-octyne to TBHP ranging from 1:0.7 to 1:2 were found to give high conversion and selectivity to the conjugated acetylenic ketone. The TBHP "loading" in this reaction is considerably lower than in many other cases,¹²⁻¹⁴ and even TBHP:substrate ratios of less than unity give acceptable yields. To obtain both high conversion and selectivity for the desired α,β -acetylenic ketone, optimal reaction conditions were determined to be CuCl₂·2H₂O:alkyne:*t*-BuOOH in a 1:25:50 ratio in *t*-BuOH at 70 °C under an O₂ atmosphere. This protocol was then applied to a wide range of other alkyne substrates bearing α -CH₂ groups, with the selective autoxidation results summarized in Table 3. In general, the oxidation

Table 2. Effect of CuCl₂·2H₂O Concentration on the Oxidation of 4-Octyne with TBHP^a


CuCl ₂ ·2H ₂ O : 4-octyne (mole ratio)	Conv. ^b (%)	Product Distribution ^c (%)	
		$\text{C}_3\text{H}_7\text{C}=\text{C}(\text{O})\text{C}_2\text{H}_5$	$\text{C}_3\text{H}_7\text{C}=\text{C}(\text{OH})\text{C}_2\text{H}_5$
1 : 10	94	97	1
1 : 25	91	97	1
1 : 50	90	88	10
1 : 75	92	77	21
1 : 100	90	78	20
1 : 200	88	68	29
Without CuCl ₂ ·2H ₂ O	56	17	80

^a 4-Octyne (4.5 mmol) and TBHP (3.15 mmol); molar ratio = 1:0.7 were used. The reaction was carried out at 70 °C under O₂ for 24 h. ^b Conversion was determined on the basis of the internal standard, *tert*-butylbenzene. ^c Product distributions were determined by GC. Small amounts of unidentified products were also observed.

to the α,β -acetylenic ketone proceeds with both high conversion and selectivity. The only major side product after 24 h is the acetylenic alcohol. In fact, if a longer reaction time was allowed, this side product could be completely converted to the α,β -acetylenic ketone. Moreover, a range of alkyne reactivities was found to correlate with the ease of C–H atom abstraction.

Symmetric internal aliphatic alkynes, such as 3-hexyne, 4-octyne, and 5-decyne, give excellent conversions and selectivities of the ketone products. The aliphatic chain length has little effect on the reactivity and selectivity. Unsymmetric internal aliphatic alkynes, such as 3-heptyne and 4-nonyne, give a pair of acetylenic ketones with approximately equal distribution, indicating that the system cannot distinguish between the two chemically similar α -CH₂ groups of the substrate. However, the oxidation of 2-decyne is regiospecific, yielding 2-decyn-3-one in 70% yield and with no products resulting from C–H abstraction from the methyl group. Terminal acetylenes also yield acetylenic ketones although the substrate reactivity is diminished. Besides the aliphatic alkynes, aromatic alkynes such as 1-phenyl-1-pentyne can be oxidized to the corresponding conjugated acetylenic ketone in good yield. The reaction conditions can also be employed for oxidation of other related substrates, such as *cis*-cyclooctene, which yields 3-cyclooctenone with lower selectivity. Introduction of adjacent carboxylate groups severely inhibits the alkyne reactivity. No apparent substrate oxidation is observed for methyl 2-octynoate or 2-octynoic acid after 24 h. By contrast, 3-hexyne-2,5-diol is rapidly converted to 3-hexyn-2-ol-5-one in high yield, and a degree of further oxidation to 3-hexyne-2,5-dione also occurs. A key point of interest in examining substrate reactivity is that the product types RC=CCH(OH)R' and RCH₂C=CCOR' are potential substrates. Our results indicate that acetylenic alcohols, while not typically as reactive as 3-hexyne-2,5-diol, are

Table 3. Oxidation of Alkynes Using Cu²⁺/TBHP under Oxygen^a

Entry	Substrate	Product	Conv. ^b (%)	Yield ^c (%)
1	C ₂ H ₅ C≡CC ₂ H ₅	CH ₃ C(O)C≡CC ₂ H ₅	91	59
2	C ₃ H ₇ C≡CC ₃ H ₇	C ₂ H ₅ C(O)C≡CC ₃ H ₇	99	74
3	C ₄ H ₉ C≡CC ₄ H ₉	C ₃ H ₇ C(O)C≡CC ₄ H ₉	95	66
4	C ₂ H ₅ C≡CC ₃ H ₇	CH ₃ C(O)C≡CC ₃ H ₇	100	37
		C ₂ H ₅ C≡CC(O)C ₂ H ₅		31
5	C ₃ H ₇ C≡CC ₄ H ₉	C ₂ H ₅ C(O)C≡CC ₄ H ₉	99	39
		C ₃ H ₇ C≡CC(O)C ₃ H ₇		37
6	CH ₃ C≡CC ₇ H ₁₅	CH ₃ C≡CC(O)C ₆ H ₁₃	84	70
7	HC≡CC ₆ H ₁₃	HC≡CC(O)C ₅ H ₁₁	61	51
8	PhC≡CC ₃ H ₇	PhC≡CC(O)C ₂ H ₅	85	78
9	C ₅ H ₁₁ C≡C-COOCH ₃	No reaction		
10	C ₅ H ₁₁ C≡C-COOH	No reaction		
11	cis-Cyclooctene		97	42
12	^d CH ₃ CHC=CCHCH ₃ OH OH	CH ₃ CHC=CCHCH ₃ OH O	100	65
		CH ₃ CHC=CCHCH ₃ O O		15

^a CuCl₂·2H₂O:substrate:*t*-BuOOH = 1:25:50 (molar ratio). Reactions were carried out at 70 °C for 24 h under O₂. ^b Conversion was determined by GC analysis using an internal standard, *tert*-butylbenzene. Byproducts were mainly acetylenic alcohols. ^c Isolated yield. ^d 10 h reaction.

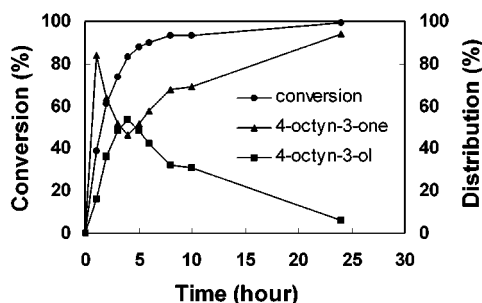
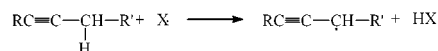
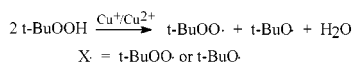
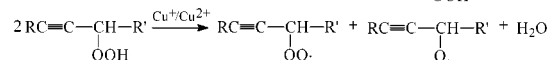
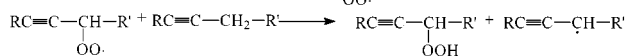
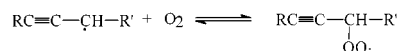
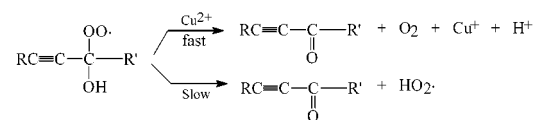
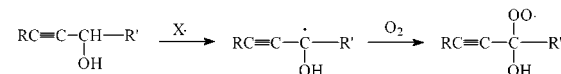
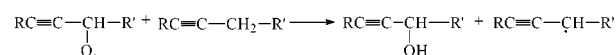
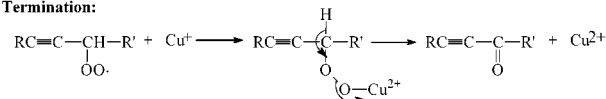


Figure 1. Kinetics of the oxidation of 4-octyne and the product distribution. (Reaction conditions: 4-octyne (4.5 mmol), *t*-BuOOH (70%, 9 mmol), CuCl₂·2H₂O (0.18 mmol), stepwise addition at 70 °C under oxygen.)

still activated for further reaction to acetylenic ketones. However, like acetylenic esters or acids, the acetylenic ketones are strongly deactivated. Since oxidation may progress to α,β -acetylenic ketones but no further, the high selectivity of the reaction is reasonably assured.

The reaction kinetics for 4-octyne is shown in Figure 1. Near complete conversion of the substrate was achieved after a relatively short time (4–5 h), giving a mixture of acetylenic alcohol and ketone. Investigation of the product distribution by GC over time showed that immediately after initiation the major product was the acetylenic ketone. The acetylenic alcohol then built up

Scheme 1**Initiation:****Propagation:****Termination:**

to a maximum, finally decreasing again. Since it was converted to ketone more slowly than it was formed,¹⁷ the reaction was allowed to react for 24 h to give a high yield of acetylenic ketone. An accelerated reaction could be achieved when the TBHP, which served as a radical reservoir, was added in fresh aliquots over the first 4 h of the reaction, rather than all at once in the beginning.

A mechanistic scheme for the conversion of alkyne to α,β -acetylenic ketone is proposed in Scheme 1. The first step is metal-catalyzed initiation, which creates butoxy (*t*-BuO·) and peroxy (*t*-BuOO·) radicals from the *t*-BuOOH.¹⁸ While Cu²⁺ was found to be highly efficient in this respect, other metal ions such as Co²⁺ could be employed with similar effect. The radicals thus formed then carry out selective H atom abstraction from the α -CH₂ group of the alkyne substrate. The resulting radical may then react with dioxygen to form an acetylenic peroxy radical, which can yield the acetylenic ketone directly via elimination or undergo further reaction to acetylenic alcohol. It is then converted to α,β -acetylenic ketone over time by acting as the substrate for a second α -C-H abstraction. The role of the metal ion in this step appears to be critical because it can catalyze the conversion of the α -hydroxyalkylperoxy radical to a α,β -acetylenic ketone.¹⁹

In summary, a convenient process based on metal-catalyzed *tert*-butyl hydroperoxide autoxidation has been developed for the conversion of alkynes to α,β -acetylenic

(17) The relative rate of oxidation of acetylene and its corresponding acetylenic alcohol is variable and depends on radical stability: for 1-phenyl-1-pentyne, no build-up of alcohol PhC≡CCH(OH)Et was found, since it was rapidly converted to the ketone PhC≡CC(O)Et (see Supporting Information).

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ketones, with high conversion and selectivity. The reaction has broad substrate applicability, and R and R' can be a variety of aliphatic or aromatic groups; it thus promises to be a useful preparative route for this important functional group conversion. Appropriate modification of the reaction conditions should also allow for the isolation of acetylenic alcohols in preparative yields and is currently under investigation.

Experimental Section

General Oxidation of Alkynes for Table 3. Copper chloride dihydrate (31 mg, 0.18 mmol), TBHP (70%, 1.23 mL, 9 mmol), and alkyne (4.5 mmol) were stirred under an oxygen atmosphere (1 atm) in *t*-BuOH (20 mL) at 70 °C for 24 h. Progress of the reaction was monitored using gas chromatography or TLC. Optimal results were obtained when the TBHP was added stepwise (four portions over hourly intervals) over the first 4 h of the reaction. After the reaction mixture was cooled to room temperature, the solvent was removed with a rotary

evaporator, and the residue was dissolved in 30 mL of diethyl ether, followed by washing with brine solution. The ether layer was subsequently dried over anhydrous calcium chloride and evaporated to dryness to give crude products. Pure products were isolated using thick TLC plates with various ratios of ethyl acetate to hexane or other mixed solvents as eluent. They were identified by ¹H and ¹³C NMR, FTIR, and mass spectrometry and compared with literature data and/or authentic samples.

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Supporting Information Available: Product distribution of the oxidation of 1-phenyl-1-pentyne. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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