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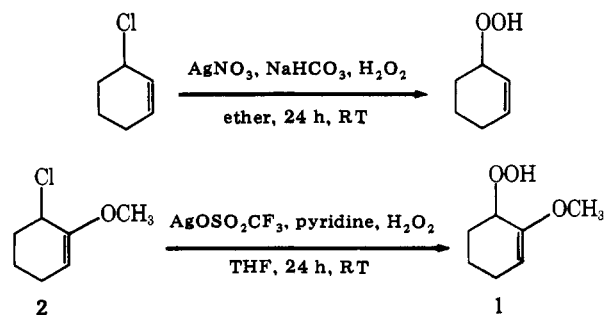## A Convenient Synthesis of Allylic Hydroperoxides

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Because of our recent investigation of the singlet oxygen "ene" reaction of 1-methoxycyclohexene,[2] we were interested in preparing the enol ether allylic hydroperoxide, 3-hydroperoxy-2-methoxycyclohexene (1). Allylic hydroperoxides have been synthesized by various methods:[3] (a) from the free-radical autoxidation of olefins, initiated thermally or photolytically; (b) from the autoxidation of organometallic compounds, particularly Grignard reagents; (c) from the reaction of olefins with singlet oxygen; (d) from the solvolysis of alkenyl sulfates (prepared in situ from equimolar quantities of alcohol and sulfuric acid) in hydrogen peroxide; (e) from the solvolysis of allylic mesylates and other sulfonate esters in basic hydrogen peroxide; and (f) from the nucleophilic displacement of allyl halides with basic hydrogen peroxide.

Methods a and c are often problematic since they yield a multiplicity of products. Isolation and purification is a serious problem with hydroperoxides in general and alkenyl hydroperoxides in particular.[2b] Because hydroperoxide 1, in addition to being allylic, is at the same time an enol ether, methods involving acidic hydrogen peroxide or acidic workups are to be avoided (method d).[4] Nor could a Grignard path (method b) be used since enol ethers react with Grignard reagents at the double bond site.[4]

We would like to report a convenient synthesis of allylic hydroperoxides via the silver ion assisted reaction of the corresponding allylic halide and hydrogen peroxide. In par-

ticular, an ether solution of 3-chlorocyclohexene,[5] silver nitrate,[6] $NaHCO_3$ (in a 1:1:2 molar ratio), and a tenfold excess of 98% H_2O_2 was stirred for 24 h at room temperature in the dark under argon.[7] Filtration and evaporation of the solvent under reduced pressure gave an almost quantitative yield of 3-hydroperoxycyclohexene.

Similarly, a THF solution of 3-chloro-2-methoxycyclohexene (2) was stirred for 1 day in the dark under argon[7] with 1 equiv of pyridine,[8] 2 equiv of silver triflate, and 15 equiv of 98% H_2O_2. Filtration and evaporation of the solvent and pyridine under high vacuum gave the desired hydroperoxide in an 80% yield.

At this juncture we would like to note that when 2 was allowed to react with H_2O_2 in the presence of silver nitrate, the yet unknown[9] 2-methoxy-2-cyclohexen-1-yl nitrate (3) was obtained, in approximately 50% yield, in addition to the allylic hydroperoxide 1. The unstable nitrate was isolated by high vacuum distillation and identified by its spectral data (see Experimental Section).

The starting allylic chloride 2[11] could not by synthesized from 1-methoxycyclohexene and N-chloro amides since enol ethers react via a polar, not free-radical, mechanism with these chlorinating agents.[4] Nor could it be prepared conveniently by the action of $Ph_3P–CCl_4$ on 3-hydroxy-2-methoxycyclohexene (4).[13] In contrast to 3-hydroxycyclohexene, which in the presence of $Ph_3P–CCl_4$ proceeded smoothly and quantitatively to the corresponding chloride, 4 yielded only 25% 2. Surprisingly, the major product was 2-methoxycyclohexanone (5), which was readily synthesized by reducing 2-methoxy-2-cyclohexen-1-one (6) with hydrogen and palladium.

Chloride 2 was successfully prepared as follows. Epoxidation of commercially available (Aldrich Chemical Co.) 2-cyclohexen-1-one (8) with either alkaline hydrogen peroxide[14] or *tert*-butyl hydroperoxide[15] affords 2,3-epoxycyclohexanone (7). The latter method is the procedure of choice since it gives the desired product in approximately 80% yield while the former gives it in 30% yield. Treatment of the epoxide with methoxide in methanol followed by neutralization and distillation gives 26–34% yield of ketone 6.[16] Reduction of 6 with diisobutylaluminum hydride (DIBAL),[17] neutralization with methanol, and distillation give alcohol 4 in 88% yield.[18] The corresponding mesylate 9 was conveniently prepared in situ according to the procedure of Crossland and Servis.[19] Displacement of the mesylate group with chloride ion, workup, and distillation gave the desired product in 75% yield.[20,21]

Both 3-hydroperoxycyclohexene and its 2-methoxy analogue (1) are readily reduced by triphenylphosphine to yield the corresponding alcohols. Thermolysis of these two hydroperoxides in the VPC injection port produced both the corresponding alcohol and ketone. The mechanism of such a thermal cleavage is discussed by Walsh[22] and Frank.[23,24]

Throughout this work most spectra were recorded using deuteriochloroform as solvent. In many cases, it was convenient to follow the progress of the reaction by NMR particularly by studying the growth and disappearance of methoxy group absorptions which show up as sharp singlets. As can be seen from Table I, however, the methoxy absorptions in $CDCl_3$

Table I. ¹H NMR Absorption (δ, ppm Me₄Si) of 3-Substituted 2-Methoxycyclohexenes
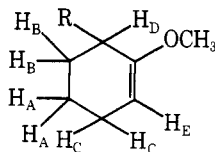
Registry no.	Compd	Solvent	R =	H_A	H_B	H_C	$-OCH_3$	H_D[c]	H_E[b]	Misc
931-57-7		CDCl₃	H	1.57	1.57	2.00	3.40	2.00	3.51	
23740-37-6	6		=O	2.00	2.43	2.43	3.58		5.90	
62796-20-7	4		OH	1.73	1.73	2.01	3.53	4.13	4.73	HO −3.10
59892-15-8	2		Cl	1.70	2.05	2.05	3.55	4.43	4.82	
62796-21-8	3		ONO₂	1.90	1.90	1.90	3.53	5.45	5.05	
62796-22-9	1		OOH	1.60	1.60	2.03	3.53	4.43	4.92	HOO ~9.17[a]
7429-44-9	5		=O[d]	1.81	2.33	1.81	3.38		1.81	CH₃OCH — 3.72
1728-36-5	2'		Br	1.75	2.13	2.13	3.54	4.62	4.85	
	6	C₆H₆	=O	1.62	2.13	2.13	3.32		5.53	
	4		OH	1.83	1.83	1.83	3.24	4.20	4.50	HO −2.98
	2		Cl	1.85	1.85	1.85	3.22	4.40	4.40	
	3		ONO₂	1.60	1.60	1.60	3.15	5.37	4.64	
	1		OOH	1.60	1.60	1.90	3.27	4.65	4.65	HOO ~9.33[a]

[a] Usually very broad and variable. [b] H_E generally comes as a clearly defined triplet. [c] H_D usually comes as a broad peak with hyperfine splitting, sometimes as a triplet. [d] Compound 6 with saturated double bond.

for many of the 3-substituted 2-methoxycyclohexenes are very close together if not identical. Benzene, as shown in Table I, has a dramatic effect on these absorptions and was often used as the NMR solvent of choice.

Experimental Section

NMR spectra were obtained on Varian A-60 and T-60 spectrometers. Infrared spectra were taken with a Perkin-Elmer Model 137 spectrometer. Mass spectra were run on an Associated Electrical Industries, Ltd., Model MS-9 mass spectrometer.

Analyses of compounds were obtained from Anacon Associates, Chelmsford, Mass. Vapor phase chromatograms were run with a Hewlett-Packard F and M Model 700, Varian Aerograph Models 90-P3, and Autoprep Model A-700 chromatographs. Peak areas were measured by disk integration and triangulation.

The 98% H_2O_2 was obtained from FMC Corp. All reactions involving 98% H_2O_2 were run with the necessary safety precautions. All operations were carried out behind a shield and in a hood with the hood cover as far down as possible. The experimenter wore safety glasses, a face shield, and thick neoprene gloves. To prevent contamination of the H_2O_2 bottle, H_2O_2 samples were poured into a graduated cylinder rather than removing them from the bottle with a pipet.

2-Methoxy-2-cyclohexen-1-ol (4). A 2-L three-necked round-bottom flask fitted with a reflux condenser (topped with argon inlet), stopper, and serum cap was charged with 30.4 g (0.24 mol) of ketone 6[16] dissolved in 600 mL of dry benzene at approximately 10 °C. The solution was magnetically stirred and kept under an argon blanket throughout the reaction. A 1 M solution (360 mL) of diisobutylaluminum hydride (DIBAL) in heptane (D. C. R. Inc.) was added to the reaction mixture which, during the course of the addition, gradually turned cloudy. After the addition, which took about 30 min, the solution was stirred at 5–10 °C for another 1 h. Dry methanol (250 mL) was then gradually added, followed by 35 g of a Na_2SO_4/H_2O paste.[25] The solution was stirred again until a white precipitate formed, at which time stirring usually ceased. An additional 500 mL of methanol was added, the precipitate was broken up, and stirring was continued for an additional 30 min. The mixture was vacuum filtered and the salts were washed eight to ten times with boiling methanol. The solvent was removed under reduced pressure and the desired product (27 g, 0.21 mol, 87.8% yield) distilled in the range 92–98 °C (15 mm): NMR (CDCl₃) δ 1.73 (m, 4 H), 2.01 (m, 2 H), 3.10 (broad peak, 1 H, hydroxyl), 3.53 (s, 3 H, methoxy), 4.13 (m, 1 H), 4.73 (triplet, 1 H, olefinic); IR (film) 3476 (s), 2956 (s), 1669 (s), 1440 (m), 1400 (m), 1375 (w), 1334 (m), 1305 (m), 1246 (w), 1213 (m), 1190 (s), 1160 (s), 1087 (s), 1066 (s), 1026 (s), 986 (s), 957 (m), 911 (m), 883 (w), 872 (m), 857 (w), 825 (m), 793 cm⁻¹ (s); MS (70 eV) m/e 128 (M⁺).

2-Methoxycyclohexanone (5).[26] A 2-g sample of 2-methoxy-2-cyclohexen-1-one (6) dissolved in 10 mL of dry ether and 0.1 g of 5% palladium on carbon were placed in a Parr hydrogenation apparatus

under 50 lb of pressure and shaken for 20 h. Filtration and evaporation of solvent gave 1.95 g of pure 5 as determined by VPC[27] (oven, 200 °C; R_f 4 min): NMR (CDCl₃) δ 1.81 (m, 6 H), 2.33 (m, 2 H), 3.38 (s, 3 H), 3.72 (m, 1 H); IR (CCl₄) 2938 (s), 1721 (s), 1442 (m), 1425 (m), 1344 (w), 1322 (w), 1304 (m), 1259 (w), 1224 (w), 1195 (s), 1146 (s), 1113 (s), 1099 (s), 1070 (m), 1034 (w), 1013 (w), 993 (w), 946 (m), 915 (w), 877 (m), 836 cm⁻¹ (w); MS (70 eV) m/e 128 (M⁺).

3-Chloro-2-methoxycyclohexene (2). A three-necked 250-mL round-bottom flask fitted with serum cap, gas inlet tube with stopcock and stopper was charged with 6.4 g (0.05 mol) of 4 and 10.5 mL (8 g, 0.075 mol) of triethylamine dissolved in 175 mL of methylene chloride. The flask was placed under an argon blanket and cooled to −20 °C in a CCl₄/CO₂ slush bath. Then 4.4 mL (6.65 g, 0.055 mol) of mesyl chloride was added over a period of 10 min and the solution was stirred for 30 more min. The reaction flask was placed in a water bath and the methylene chloride and excess triethylamine were distilled (0.1 mm) gradually into a liquid nitrogen trap. Approximately 150 mL of solvent was removed in about 1 h. Then 175 mL of acetone and 21 g (0.05 mol, excess) of lithium chloride were added and the solution was stirred for 4 h at room temperature. Ether (400 mL) was added to precipitate the salts and the solution was vacuum filtered and concentrated down under reduced pressure to a viscous oil. More ether was added and the solution was dried over MgSO₄. Filtration, removal of solvent under reduced pressure, and distillation (77–78 °C, 8 mm) gave 5.5 g of product (75% yield): NMR (CDCl₃) δ 1.70 (m, 2 H), 2.05 (m, 4 H), 3.55 (s, 3 H, methoxy), 4.43 (t with hyperfine splitting, 1 H), 4.82 (t, 1 H); IR (film) 2959 (s), 2841 (m), 1662 (s), 1435 (m), 1373 (s), 1330 (w), 1296 (w), 1258 (w), 1232 (s), 1214 (s), 1186 (s), 1166 (s), 1087 (m), 1040 (m), 1024 (s), 960 (w), 933 (w), 876 (m), 803 (m), 793 (m), 708 cm⁻¹ (s); MS (70 eV) m/e 146 (M⁺), M⁺ + 2 is approximately 33% of parent peak.

Preparation of Silver Triflate. A suspension of 12.6 g (0.109 equiv) of Ag₂O[28] in 125 mL of water at 15 °C was stirred vigorously while triflic acid, CF_3SO_3H (3M Corp., Acid FC24),[29] was slowly added. The solution gradually turned from black to a cloudy beige and the addition was stopped when the pH reached approximately 2. The mixture was filtered and the water removed under reduced pressure at 60 °C. The white residue was dissolved in boiling benzene and allowed to boil for a while longer to remove any water. Hexane was then added and the solution placed in the refrigerator. The white needles were placed in a vacuum desiccator and the benzene coordinated during crystallization was removed in vacuo (28 h), yield 23.3 g (83%). Silver triflate should be handled wearing gloves since like silver nitrate it discolors the skin.

General Procedure for the Preparation of Allylic Hydroperoxides. A three-necked 100-mL round-bottom flask fitted with thermometer, dropping funnel, and argon inlet was charged with 50 mL of THF, 6 g (0.04 mol) of silver triflate, and 1.6 g (0.02 mol) of pyridine. The reaction vessel was wrapped in aluminum foil to exclude light.[7] The solution was magnetically stirred and cooled to 6 °C in an ice bath. To the chilled solution 7.5 mL (10.8 g, 0.32 mol) of 98% H_2O_2

was slowly pipetted in. The temperature rose to 10 °C during the 15-min addition and then cooled back down to 6 °C. Then a 0.02-mol sample of the allylic chloride dissolved in 10 mL of THF was added dropwise to the clear solution at a moderate rate from the dropping funnel. A white precipitate (AgCl) formed almost immediately but the reaction was allowed to continue at room temperature in the dark under argon for 24 h. The reaction mixture was gravity filtered into a separatory funnel containing several chips of ice. The THF solution was diluted with ether, extracted several times with iced saturated NaHCO₃ solution, and dried over MgSO₄. Most of the ether and the THF was removed under reduced pressure and the remaining impurities (THF, pyridine, and starting material) were distilled off under high vacuum at room temperature. The remaining viscous liquid is the desired hydroperoxide.

A. 3-Hydroperoxycyclohexene. This allylic hydroperoxide was prepared in an 83% yield from 3-chlorocyclohexene (Aldrich) as described above in the general procedure. The reaction was followed by VPC[27] (oven, 160 °C), the chloride peak (R_f 2 min) gradually disappearing with the concomitant growth of peaks corresponding to 2-cyclohexen-1-one and -1-ol (R_f ~5.5 min). The hydroperoxide could be distilled under high vacuum (0.1 mm) into a receiver cooled with liquid nitrogen by cautiously warming the distillation flask with a 40 °C water bath [lit. bp 47–48 °C (0.2 mm),[30] 39–40 °C (0.1 mm)[31]]: NMR (CDCl₃) δ 1.83 (m, 6 H), 4.5 (m, 1 H), 5.88 (m, 2 H, olefinic), 9.13 (broad s, 1 H, hydroperoxide).

B. 3-Hydroperoxy-2-methoxycyclohexene (1). Enol ether allylic hydroperoxide 1 was obtained in 75% yield from chloride 2 using the above general procedure. It can be stored for long periods of time unchanged at −20 °C under argon: NMR (CDCl₃) δ 1.60 and 2.03 (overlapping multiplets, 6 H, probably 4 H and 2 H, respectively), 3.53 (s, 3 H, methoxy), 4.43 (t, 1 H), 4.92 (t, 1 H), 9.17 (broad singlet, variable, 1 H, hydroperoxy); IR (neat) 3400 (m), 2941 (s), 1717 (w), 1660 (s), 1600 (w), 1428 (m), 1370 (m), 1329 (w), 1316 (w), 1292 (w), 1254 (w), 1212 (s), 1189 (s), 1165 (s), 1156 (s), 1087 (m), 1064 (m), 1026 (m), 971 (m), 922 (w), 877 (w), 803 (m), 710 cm⁻¹ (w). The absorption at 3400 cm⁻¹ is due to the hydroperoxy group, while the 1660 cm⁻¹ absorption is attributable to the vinyl ether carbon–carbon double bond.

Anal. Calcd for C₇H₁₂O₃: C, 58.32; H, 8.39. Found: C, 58.28; H, 8.25.

C. 2-Methoxy-2-cyclohexen-1-yl Nitrate (3). When a AgNO₃/ether/NaHCO₃ system replaced the AgO₃SCF₃/THF/pyridine system in the general procedure above, in the case of 3-chlorocyclohexene, the results were essentially unchanged. In the instance of chloride **2**, workup, evaporation of the ether under reduced pressure, and distillation of the residue at 0.005 mm at room temperature into a dry ice cooled receiving flask gave a 50% yield of a compound whose spectral data and combustion analysis were consistent with 2-methoxy-2-cyclohexenyl nitrate. The compound gradually decomposed and turned yellow upon standing in air at room temperature. The compound remaining in the distillation flask proved to be hydroperoxide **1**: NMR (CDCl₃) δ 1.90 (m, 6 H), 3.53 (s, 3 H), 5.05 (t, 1 H), 5.45 (m, 1 H); IR (neat) 2968 (m), 1741 (m), 1675 (m), 1634 (s), 1445 (m), 1380 (m), 1334 (w), 1304 (m), 1279 (s), 1217 (s), 1195 (m), 1177 (m), 1164 (m), 1132 (w), 1097 (m), 1056 (m), 1029 (m), 973 (m), 948 (m), 926 (m), 860 (s), 813 (w), 802 (w), 756 (w), 716 (w), 691 cm⁻¹ (w). The 1634 and 1279 cm⁻¹ absorptions are attributable to the –ONO₂ group. MS (70 eV) *m/e* 173 (M⁺), 111 (M⁺ − NO₃).

Anal. Calcd for C₇H₁₁NO₄: C, 48.55; H, 6.40. Found: C, 48.05; H, 6.40.

Registry No.—Silver triflate, 2923-28-6; 3-hydroperoxycyclohexene, 4845-05-0; 3-chlorocyclohexene, 2441-97-6.

References and Notes

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(6) Silver triflate may also be used (vide infra); when, however, silver acetate was utilized, a 50% yield of 3-acetoxycyclohexene was obtained in addition to the desired allylic hydroperoxide.
(7) These precautions were taken to prevent the reduction of the AgCl salt, which precipitates out as Ag⁰. The latter in turn can catalyze the decomposition of the hydrogen peroxide or hydroperoxide. In one run, in which the silver reaction was not run in the dark, the hydroperoxide formed from

3-chlorocyclohexene ignited spontaneously after isolation and concentration.
(8) The reaction proved much more rapid in this case when pyridine was used instead of bicarbonate.
(9) A synthesis, in low yield, of 2-cyclohexen-1-yl nitrate from cyclohexene, ferrous sulfate, and cupric nitrate has been reported.[10] The major product in that preparation was 2-cyclohexen-1-one and the reaction presumably proceeds via a free-radical process.
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(18) Interestingly enough alcohol 4 boils lower and has a shorter retention time on a Carbowax 20M VPC column than the corresponding ketone **6**, due to intramolecular hydrogen bonding.
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(20) (a) The ethoxy analogue of **2** has been synthesized[20b] by heating chlorocyclohexanone diethyl acetal with quinoline phosphate at an oil bath temperature of 170–190 °C with a gradually falling pressure of 20–90 mm [bp 92–96 °C (15 mm)]. (b) Winthrop Chemical Co., U.S. Patent 2 119 802 (1934), p 3, lines 19–31.
(21) The NMR spectrum of compound 2 was nearly identical with that of the corresponding bromo analogue, prepared according to the instructions of Garbisch.[12] As would be expected, the only observable difference occurred for the allylic hydrogen α to the halogen (see Table I).
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(27) 9 ft × 0.25 in. aluminum column packed with 20% Carbowax 20M on Chromosorb W AW DMCS; helium carrier gas flow rate 85 mL/min; injector 200 °C; thermal detector 250 °C.
(28) Silver acetate may also be used.
(29) THe 3M Corp. technical information circular (April 8, 1969) lists the following properties: bp 162 °C (760 mmHg), 84 °C (43 mm), 54 °C (8 mm), density 1.696 (24.5 °C), formula weight 150.02, colorless liquid which fumes in moist air.
(30) E. H. Farmer and A. Sundralingam, *J. Chem. Soc.*, 121, 132 (1942).
(31) L. Bateman and G. Gee, *Proc. R. Soc. London, Ser. A.*, **195**, 376, 382 (1948).

Asymmetric Induction in the Synthesis of Thiophene-Containing Steroidlike Molecules via Olefinic Cyclization. Precoiling as Model Description for the Stereochemical Course of the Reaction

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Recently, Corvers et al.[1a] published the preparation of heterocyclic steroids with thiophene as A ring via a cationic