# Synthesis of α-Hydroperoxy Esters by Singlet Oxygenation of Ketene Acetals[1]

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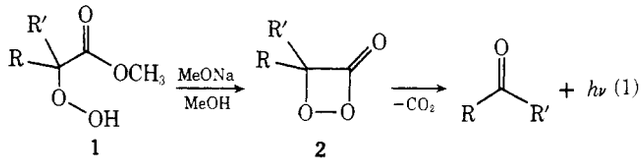
*tert*-Butyl-(**4a**) and 1-adamantylketene methyl trimethylsilyl acetals (**4b**) quantitatively singlet-oxygenate under photosensitization to their respective methyl trimethylsilyl peroxyacetates **3a** and **3b.** Desilylation with methanol affords the corresponding α-hydroperoxy esters **1a** and **1b** in high yield. The dimethylketene methyl trimethylsilyl acetal (**4c**) suffers competitive ene reaction on photooxygenation, but under controlled conditions good yields of the corresponding α-silylperoxy ester **3c** can be obtained. Similarly, the diphenylketene acetal **4d** leads also to the expected α-silylperoxy ester **3d,** but some (2 + 4) cycloaddition takes place concurrently. In both cases the corresponding α-hydroperoxy esters **1c** and **1d** were isolated and purified after methanolysis.

α-Hydroperoxy esters **1** have been shown to undergo base-catalyzed decomposition with enhanced chemiluminescence in the presence of fluorescers presumably energized by the "high-energy" α-peroxylactones **2** (eq 1)[3]. In view of

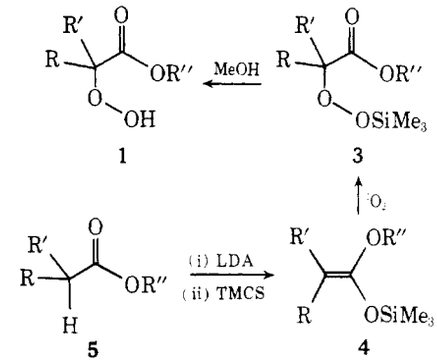



our interest in developing efficient and convenient preparative methods for α-peroxylactones **2**,[4] we considered exploiting the sequence in eq 1 as a potential route to α-peroxylactones. Of course, α-hydroperoxy esters **1** with active leaving groups would be required which would permit running the base-catalyzed cyclization under sufficiently mild conditions, e.g., subambient temperature, nonprotic media, etc., to isolate the labile α-peroxylactones.

Present methods of preparation of α-hydroperoxy esters **1** either involve direct base-catalyzed oxygenation of carboxylic esters or esterification of α-hydroperoxy acids with diazoalkanes.[5] Both methods are of limited value for our purpose since with esters containing activated leaving groups, the intermediary α-peroxy anion, formed on α-oxygenation of the ester enolate, would cyclize in situ to the α-peroxylactones. Their isolation from this complex reaction mixture would be expected to be difficult. In the esterification of the α-hydroperoxy acids with diazoalkanes or other mild esterification agents, the α-hydroperoxy acids are labile compounds which are not very readily available.[5b,6] We required, therefore, a general and convenient method for the preparation of α-hydroperoxy esters **1.**

We reported previously[4] that ketene bis(trimethylsilyl) acetals singlet-oxygenate with silatropic rearrangement to the corresponding trimethylsilyl α-trimethylsilylperoxy esters in high yield. Desilylation with methanol at subambient temperatures releases the free α-hydroperoxy acid quantitatively. In principle, it should be possible to adapt this synthetic sequence for the preparation of α-hydroperoxy esters **1** from their corresponding esters **5** via their ketene alkyl trimethylsilyl acetals **4** (eq 2). In fact the alkyl α-trimethylsilylperoxy esters **3** in their own right are attractive precursors to α-peroxylactones since the corresponding α-peroxy anion should be readily accessible by fluoride ion-catalyzed desilylation in neutral, nonprotic media.[7] We now report on the feasibility of this synthetic strategy, constituting a convenient preparation of methyl α-hydroperoxy esters **1** and methyl α-trimethylsilylperoxy esters **3.** The results are collected in Tables I–III.

The ketene methyl trimethylsilyl acetals **4a–d** were pre-




**a**, R = *t*-Bu; R′ = H; R″ = Me
**b**, R = 1-Ad; R′ = H; R″ = Me
**c**, R = Me; R′ = Me; R″ = Me
**d**, R = Ph; R′ = Ph; R″ = Me

pared from their corresponding methyl esters by α-lithiation with lithium diisopropylamide (LDA), followed by silylation with excess chlorotrimethylsilane.[8] As Table I shows, the yields are high, except for **4c** which due to its great volatility was lost in part during solvent (THF) removal.

As expected,[4b] the singlet oxygenation of ketene acetal **4a** (R = *t*-Bu, R′ = H, R″ = Me) worked quantitatively, giving on fractional distillation at reduced pressure the α-silylperoxy ester **3a** in 93% yield and 99.9 ± 0.5% purity by iodometry. It was characterized on the basis of its spectral data (Table II) and correct elemental analysis. Furthermore, on desilylation with methanol the expected methyl α-hydroperoxy ester **1a** was obtained essentially quantitatively (Table III), identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.

The singlet oxygenation of the 1-adamantyl derivative **4b** also proceeded well (Table II), but in view of the low volatility of the α-silylperoxy ester **3b,** on attempted purification by fractional distillation at reduced pressure it decomposed. However, desilylation with methanol and subsequent fractional recrystallization from $CH_2Cl_2$/pentane (1:4) gave the analytically pure α-hydroperoxy ester **1b** in 69%, correct elemental analysis, and the expected spectral data (Table III).

In the case of the dimethylketene acetal **4c** the competing ene reaction with singlet oxygen[9] presented difficulties. Employing a variety of solvents such as $CCl_4$, $CFCl_3$, $CDCl_3$, $CH_2Cl_2$, $CD_3CN$, $C_6D_6$, and $CS_2$, a temperature range from −78 to +10 °C, and the sensitizers tetraphenylporphyrin (TPP) and Rose Bengal, optimal yields (by NMR monitoring) of 80% silatropic singlet oxygenation were achieved with $CH_2Cl_2$ at −5 °C and TPP as sensitizer (Table II). The remaining 20% was mainly peroxymethacrylic acid (**6**) and unidentified decomposition products, formed by ene singlet oxygenation and hydrolytic desilylation by adventitious water

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**Table I. Yields and Physical and Spectral Data of Ketene Methyl Trimethylsilyl Acetals 4**

| | Registry no. | $R_1R_2CC(OMe)OSiMe_3$ (4) $R^1$ | $R^2$ | Yield, % | bp, °C (mm),[a] $n^{25}D$ | IR($CCl_4$)[b] $\nu_{C=O}$, $cm^{-1}$ | NMR (60 MHz) δ ($CCl_4$, $Me_4Si$) $OSiMe_3$ | OMe | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **4a** | 40195-22-0 | *t*-Bu | H | 86 | 79–81 (31), 1.4094 | 1660 | 0.30 (9 H, s) | 3.55 (3 H, s) | 3.70 (1 H, s) | 1.15 (9 H, s) |
| **4b** | 64771-60-4 | 1-Ad | H | 84 | 88–92 (0.1), 1.4842 | 1660 | 0.30 (9 H, s) | 3.50 (3 H, s) | 3.40 (1 H, s) | 1.5–2.1 (15 H, m) |
| **4c** | 31469-15-5 | Me | Me | 62[c] | 54 (46), 1.4146 | 1700 | 0.30 (9 H, s) | 3.55 (3 H, s) | 1.60 (3 H, s) | 1.70 (3 H, s) |
| **4d** | 31469-19-0 | Ph | Ph | 92 | 117–119 (0.15), 1.5541 | 1630 | 0.20 (9 H, s) | 3.65 (3 H, s) | 7.3 (10 H, m) | |

[a] Reference 8. [b] Ketene acetal double bond is of medium intensity. [c] Low yield due to volatility loss.

**Table II. Yields and Physical and Spectral Data of Methyl α-Trimethylsilyl Peroxyacetates 3**

| | Registry no. | $R_1R_2C(OOSiMe_3)COOMe$ $R^1$ | $R^2$ | Yield, % | bp, °C (mm) | Peroxide titer, % | IR($CCl_4$) $\nu_{C=O}$, $cm^{-1}$, | NMR (60 MHz) δ ($CCl_4$, $Me_4Si$) OSiMe | OMe | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **3a** | 64771-61-5 | *t*-Bu | H | 93[a] | 65 (6) | 99.9 | 1760, 1740 | 0.25 (9 H, s) | 3.75 (3 H, s) | 1.05 (9 H, s) | 4.1 (1 H, s) |
| **3b** | 64771-62-6 | 1-Ad | H | 80[b] | *e* | 95 | 1760, 1730 | 0.25 (9 H, s) | 3.75 (3 H, s) | 1.6–2.3 15 H, m) | 3.95 (1 H, s) |
| **3c** | 64771-63-7 | Me | Me | 80[c] | *e* | | 1745 | 0.15 (9 H, s) | 3.65 (3 H, s) | 1.35 (6 H, s) | |
| **3d** | 64771-64-8 | Ph | Ph | 70[d] | *e* | | 1745 | 0.20 (9 H, s) | 3.4 (3 H, s) | 7.0–7.6 (5 H, m) | |

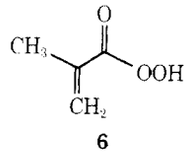
[a] Correct elemental analysis. [b] For conditions of singlet oxygenation consult General Procedure. [c] By NMR; remainder 20% are ene products and unidentified decomposition products; for this optimal yield the photooxygenation was performed in $CH_2Cl_2$ at −5 °C and TPP as sensitizer. [d] By NMR; remainder 30% are (2 + 4) cycloadducts; for this optimal yield the photooxygenation was performed in $CCl_4$ at +5 °C and TPP as sensitizer. [e] On attempted purification by fractional distillation product decomposed.

**Table III. Yields and Physical and Spectral Data of Methyl Hydroperoxyacetates 1**

| | Registry no. | $R_1R_2C(OOH)COOMe$ $R^1$ | $R^2$ | Yield, % | bp, °C (mm) | Peroxide titer, % | IR ($CCl_4$), $cm^{-1}$ $\nu_{OOH}$ | $\nu_{C=O}$ | NMR (60 MHz) δ ($CCl_4$, $Me_4Si$) OOH | OMe | $R^1$ | $R^2$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | 64771-65-9 | *t*-Bu | H | 76 | 59–60 (2.5)[a] | 99 | 3500 | 1740 | 6.65 (1 H, s) | 3.7 (3 H, s) | 4.1 (1 H, s) | 0.95 (9 H, s) |
| **1b** | 64771-66-0 | 1-Ad | H | 69 | mp 95–6 °C[a] | 100 | 3550–3480 | 1740 | 8.75 (1 H, s) | 3.7 (1 H, s) | 3.95 (1 H, s) | 1.5–2.1 (15 H, m) |
| **1c** | 64771-67-1 | Me | Me | 80 | 44–5 (15)[b] | 95 | 3100–3600 | 1740 | 4.8 (1 H, s) | 3.75 (3 H, s) | 1.45 (6 H, s) | |
| **1d** | 57272-44-3 | Ph | Ph | 72 | mp 64–5 °C[b] | 99 | 3200–3600 | 1730 | 9.6 (1 H, s) | 3.75 (3 H, s) | 7.15 (10 H, s) | |

[a] Correct elemental analysis. [b] Authentic samples prepared by $CH_2N_2$ methylation of the corresponding α-hydroperoxy acids (O. Cueto, unpublished results).

and identified by its IR and NMR spectra. Attempted separation of the singlet oxygenated product mixture by fractional

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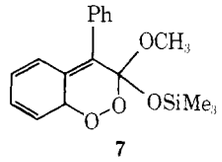


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distillation at reduced pressure led to vigorous decomposition. Consequently, the product mixture was desilylated with methanol and the α-hydroperoxy ester **1c** was isolated and purified by fractional distillation at reduced pressure (Table III). It was identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.

Also the singlet oxygenation of the diphenylketene **4d** turned out to be problematic in view of the competing (2 + 4) cycloaddition, amply documented for aryl enol ethers.[10] The IR as well as the NMR revealed that the (2 + 4) cycloadduct **7** had formed. An optimal yield (70%) of silatropic singlet oxygenation of **4d** was obtained using carbon tetrachloride at +5 °C and TPP as sensitizer (Table II). Attempted isolation and purification by fractional distillation at reduced pressure led to decomposition. Thus, the singlet oxygenated product mixture was desilylated with methanol and the analytically pure α-hydroperoxy ester **1d** was isolated and purified by fractional recrystallization in 72% yield (Table III). It was

identical with an authentic sample prepared by methylation of the corresponding α-hydroperoxy acid with diazomethane.

Our results show that a variety of α-hydroperoxy esters **1** can be prepared in good to excellent yields via the synthetic sequence outlined in eq 2. We are extending this method to α-hydroperoxy esters with activated leaving groups as synthons for the labile α-peroxylactones **2**.

## Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were taken on a Hitachi Perkin-Elmer R-24B instrument and IR spectra on a Perkin-Elmer Infracord 237B. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reagents, solvents, and starting materials were purchased from standard sources and purified according to literature procedures. Esters **5** were prepared following published methods and purified rigorously to match literature physical constants and spectral data.[11]

**Ketene Trimethylsilyl Methyl Acetals 4 (General Preparation). α-Lithiation.** A 250-mL, two-necked, round-bottomed flask, provided with a magnetic spinbar and a rubber septum, was connected to a nitrogen manifold and flame-dried while flushing with dry nitrogen. While under a $N_2$ atmosphere, a solution of 283 mmol of dry diisopropylamine (freshly distilled from $CaH_2$) in 50 mL of dry THF (freshly distilled from benzophenone ketyl radical) was syringed into the flask and dry ice cooled to −78 °C. While being stirred magnetically 10 mL of *n*-BuLi (2.55 N in hexane) was syringed dropwise into the flask. The solution was stirred 10 min at −78 °C, warmed up to room temperature (ca. 30 °C), and kept at room temperature for 10 min. The lithium diisopropylamide (LDA) solution was again dry ice cooled to −78 °C and 23 mmol of the ester **5** in 10 mL of dry THF was syringed dropwise into the LDA solution while the solution was stirred. The α-lithiocarboxylate solution was kept at −78 °C for 45 min and used for the silylation as described below.

**Silylation:** Into the freshly prepared (as described above) α-lithiocarboxylate solution was syringed 25.3 mmol of chlorotrimethylsilane (purged rigorously with dry $N_2$ to displace adventitious HCl) within 45 min while the solution was being stirred at −78 °C. The reaction mixture was allowed to warm up to room temperature (ca. 30 °C) and the THF was rotoevaporated (25 °C (20–30 mm)). The residue was triturated with 2 × 30 mL of dry benzene (freshly distilled from benzophenone ketyl radical) and filtered under a nitrogen atmosphere. The combined benzene triturates were rotoevaporated (25 °C (20–30 mm)) and the crude oil was fractionally distilled at reduced pressure. The yields and physical and spectral data for the ketene acetals **4** are collected in Table I.

**Methyl Trimethylsilyl Peroxyacetates 3 (General Photooxygenation).** A 100-mL, pear-shaped flask with a side arm which was capped with a rubber septum was connected to a nitrogen manifold. The flask was flame dried under reduced pressure while flushing with nitrogen and charged with a solution of 20 mmol of the acetal **4** in 20 mL of $CCl_4$, containing 2 mg of tetraphenylporphyrin (TPP). The solution was cooled to 0 °C with an ice bath and while passing a vivid stream of dry oxygen gas by means of a 15G stainless steel capillary, introduced through the rubber septum-capped side arm to the bottom of the flask, the contents were irradiated directly with a 400 W sodium lamp (General Electric). The reaction progress was monitored periodically by IR, following the disappearance of the 1660 $cm^{-1}$ ketene acetal band. Usually within 60–90 min photooxygenation was completed, the solvent rotoevaporated (25 °C (80 mm)) and the residue worked up by fractional distillation at reduced pressure in the case of volatile silylperoxy esters or directly methanolyzed to the hydroperoxy esters in the case of unstable, involatile products. The results are summarized in Table II.

**Methyl α-Hydroperoxyacetates 1 (General Methanolysis).** A 50-ml, stoppered Erlenmeyer flask, provided with magnetic spinbar, was charged with 20 mL of methanol and cooled to 0 °C by means of an ice bath. While being stirred and cooled 4.64 mmol of silylperoxy ester **3** was syringed into the methanol and allowed to stir overnight. The methanol was rotoevaporated (10 °C (10 mm)) and the crude product was fractionally distilled or recrystallized. The results are summarized in Table III.

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**Registry No.**—**5a,** 10250-48-3; **5b,** 27174-71-6; **5c,** 547-63-7; **5d,** 3469-00-9; chlorotrimethylsilane, 75-77-4.

## References and Notes

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# Steric Effects. 11. Substituents at Sulfur

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SX groups, where X is alkyl, were shown to have constant electrical effects. Steric parameters, $\upsilon_{SX}$, for eight SR groups were calculated from rates of alkaline hydrolysis of alkyl thiolacetates in 40% v/v dioxane–water at 35 °C by the equation: $\upsilon_{SX} = 1.14 \log k_{SX} + 2.06$. The $\upsilon_{SX}$ parameters were used to correlate rate data for the acid- and base-catalyzed hydrolyses of alkyl thiolacetates with the modified Taft equation. The magnitude of the $\psi$ values obtained is discussed. Rate and equilibrium data for an additional 17 sets of reactions involving alkyl groups attached to sulfur have been correlated with the $\upsilon_{SX}$, $\upsilon_X$, and $\upsilon_X'$ constants by means of the modified Taft equation. Of the 24 sets studied, 23 gave significant correlations, leading to the conclusion that the effect of alkyl group substitution on sulfur is largely or wholly steric in nature.

In our last two papers in this series, we have developed steric substituent constants for alkoxy groups[1] and for alkylamino and dialkylamino groups.[2] In this paper, we extend our investigation to the problem of the definition of steric substituent constants for alkylthio groups. For this purpose, let us consider the effect of alkyl groups upon the rates of acid-catalyzed and base-catalyzed hydrolysis of alkyl thiolacetates. In addition to the steric effects of interest to us, we

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