A Convenient and Efficient Preparation of Aromatic α-Hydroperoxy Acids via Oxygenation of α-Lithio Enolates, Prepared by Direct α-Lithiation of Arylacetic Acids[1]

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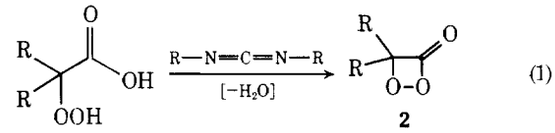
Direct α-lithiation of aromatic acetic acids by *n*-butyllithium in THF at −40 °C affords essentially quantitatively lithium α-lithiocarboxylates. The method can be employed as a convenient titration of alkyllithiums. α-Deuteration and bistrimethylsilylation of the α-lithiocarboxylates takes place essentially quantitatively. These are reliable electrophiles for the quantitative determination of the α-lithiocarboxylates. Direct oxygenation with molecular oxygen at room temperature affords good yields of the respectiye α-hydroxy acids, while reaction with molecular oxygen at dry ice temperature by inverse addition is an excellent method for the preparation of α-hydroperoxy acids derived from arylacetic acids.

α-Hydroperoxy acids **1**, which on cyclodehydration serve as precursors to α-peroxylactones **2** (eq 1),[3] are extremely



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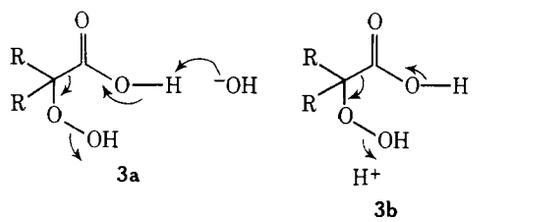
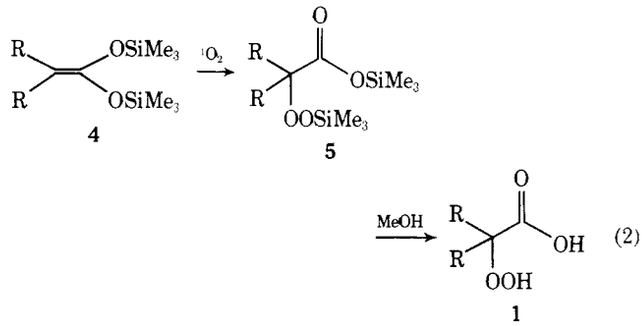


base- and acid-sensitive compounds in view of the facile Grob-type fragmentations[4] depicted in the respective transition states **3a** and **3b**. Since these decarboxylations efficiently destroy the α-hydroperoxy acids **1**, it was essential to circumvent this problem by working under neutral conditions. We took advantage of the oxygenophilic propensity of the trimethylsilyl group and prepared a number of α-hydroperoxy acids **1** by singlet oxygenation of ketene bis(trimethylsilyl) acetals **4** and subsequent desilylation of the peroxy ester **5** with methanol (eq 2). Analogous silatropic shifts have been ob-



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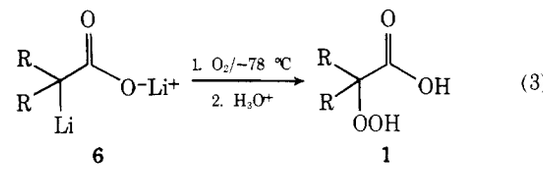
served in the singlet oxygenation of trimethylsilyl enol ethers.[5]

This novel α-hydroperoxylation lacks unfortunately generality since the classical prototropics shifts (ene reaction) compete with the silatropic shift when R is a nontertiary alkyl group[6] in the ketene acetal **4**. When R is an aromatic group, the classical [2 + 4] cycloaddition of the styryl unit with singlet oxygen competes.[7]

Recently, we and others[8] have shown that α-lithio enolates can be directly oxygenated to afford α-hydroperoxy acids **1** after acidification (eq 3). Unfortunately, this most direct α-



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oxygenation is limited to nonaromatic substrates since an attempt to α-oxygenate α-lithio-α-phenylacetate gave only decomposition and reduction products.[8b] To suppress the Grob fragmentation process, since benzaldehyde was the major product, we did not use hexamethylphosphoramide (HMPA) and pumped off the diisopropylamine prior to α-oxygenation. While this process gave significantly improved results for the lower α-alkyl- and α,α-dialkylacetic acids, only poor yields of impure α-hydroperoxy acids could be realized for phenylacetic acid.[9] It was clear to us that even traces of amines exerted detrimental effects in the preparation of α-hydroperoxy acids derived from arylacetic acids via α-lithiation with lithium diisopropylamide (LDA).

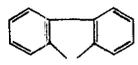
Although aliphatic carboxylates form ketones on treatment with alkyllithiums,[10] Ivanov and colleagues demonstrated[11] that arylacetates can be α-lithiated with alkyllithiums directly; however, generally the yields were poor (19–35%). It was not clear whether the metalation process worked poorly or whether the titration of the α-lithioacetates with electrophiles was inefficient. Since it was critical for the α-oxygenation process that the α-lithio enolates were formed in high purity and high yield, in order not to encumber the purification of the labile α-hydroperoxy acids **1**, we undertook the present investigation on the α-lithiation of arylacetic acids, and for comparison alkylacetic acids, with *n*-butyllithium.[12] Electrophilic substitution with deuterium oxide, trimethylsilyl chloride, benzophenone, and molecular oxygen was used for diagnosing the efficiency of α-lithioacetate formation. In the latter case, inverse addition at low temperature should afford α-hydroperoxy acids,[8] while normal addition at room temperature should lead to α-hydroxy acids.[13]

Experimental Section

All commercially available solvents, starting materials, and authentic samples for product comparison were rigorously purified according to literature procedures. Boiling points and melting points are uncorrected; the latter were determined on a Thomas-Hoover melting apparatus. The infrared spectra were measured on a Perkin-Elmer Model 237B Infracord. The NMR spectra were taken on a Varian T60 or Hitachi Perkin-Elmer R-24B spectrometer.

α-Lithiation. A 100-ml round-bottom flask with side arm, provided with a spinbar, was attached to a nitrogen manifold and protected with a rubber septum. After flame drying under a nitrogen atmosphere, by means of a calibrated syringe 1.4 mmol of the carboxylic acid in 30 ml of anhydrous THF was introduced through the serum

Table I. Yields of Electrophilic Substitution Products of Lithium α-Lithiocarboxylate (6) in THF

System	R_1	R_2	6 % yield[a]	7 % D[b]	8 % yield	4 % yield	9 % yield	1 % yield	1 % perox[d]
a	Ph	H	83	95	81	80	86	82	96
b	Ph	Ph	85	100	0[c]	77	75	67	95
c			87	95	0[c]	95[b]	70	66	92
d	*t*-Bu	H	77	58	14	32[b]			
e	Me	Me	69	50	28[b]	18[b]			

[a] Calculated on the basis of recovered acid. [b] Determined by NMR. [c] Not even traces of β-hydroxy acids could be detected by TLC. [d] Determined by iodometry; recrystallized pure product ca. 30%.

cap. The contents were cooled to −60 °C by means of a dry ice/acetone bath and while stirring magnetically a stoichiometric amount of standardized *n*-butyllithium in *n*-hexane (1.8–2.4 M) was injected dropwise by means of a calibrated syringe (ca. 5 min) to prepare the lithium carboxylate. After 60 min the reaction mixture was warmed to −40 °C and the second mole of *n*-BuLi was added dropwise from the same syringe. During this stage the pale yellow lithium carboxylate solution turned an intense dark red color, indicating that the α-lithiocarboxylate had formed. The reaction mixture was stirred for an additional 100 min at −40 °C to complete the α-lithiation and used for the electrophilic substitution reaction described below.

α-Deuteration. To the above prepared lithium α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C, about a 200 molar excess of deuterium oxide (99.8% deuterium) by means of a syringe. The α-lithiocarboxylate color immediately disappeared. After 60 min of stirring at −20 °C (a control experiment showed that hydrogen–deuterium exchange at the α position was negligible!), the solvent and excess D_2O was rotoevaporated (ca. 10 °C, 2 mm) and the residue acidified with 10% aqueous HCl, extracted with 4 × 5 ml of ether, and dried over $MgSO_4$. Rotoevaporation (ca. 30 °C, 25 mm) of the ether and NMR analysis of the crude α-deuterated acid **7** for residual α hydrogens gave the percent deuteration summarized in Table I. Fractional distillation or recrystallization was not necessary since the recovered acid was pure by NMR.

α-Diphenylhydroxymethylation. To the above prepared α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C by means of a dry ice/acetone bath, stoichiometric amounts of benzophenone in 10 ml of anhydrous THF by means of a syringe and the solution was stirred for 10 h at room temperature (ca. 30 °C). The THF was rotoevaported (ca. 30 °C at 20 mm), the residue hydrolyzed with 10% HCl and extracted with 4 × 5 ml of CH_2Cl_2, and the combined extracts dried over $MgSO_4$, and rotoevaporation (ca. 30 °C 25 mm) of the solvent afforded the crude α-hydroxy acid **8**. Final purification by recrystallization or fractional distillation at reduced pressure gave the pure β-hydroxy acids **8**, confirmed by the reported physical constants and ir and NMR spectral data. The results are summarized in Table I.

O,O-Bistrimethylsilylation. To the above prepared α-lithiocarboxylate solution in THF was added dropwise, while stirring magnetically and cooling at −40 °C by means of a dry ice/acetone bath, a 10% molar excess of trimethylsilyl chloride by means of a syringe and the solution was stirred at −40 °C for 2 h. The THF was rotoevaporated (ca. 30 °C, 20 mm) and the residue molecularly distilled at 0.01 mmHg to afford the pure ketene acetal **4** (Table I).

α-Hydroxylation. Through the above prepared α-lithiocarboxylate solution in THF was bubbled a fast stream of dry oxygen gas by means of a stainless steel capillary (12 G), while stirring magnetically at ca. 20 °C. The α-oxycarboxylate precipitated from the reaction mixture. The THF was rotoevaporated (ca. 30 °C, 20 mm) and the residue hydrolyzed with 10% aqueous HCl. Extraction with 4 × 5 ml of ether, drying of the combined ether extracts with anhydrous $MgSO_4$, rotoevaporation (ca. 30 °C, 25 mm) of the ether, and recrystallization gave the pure α-hydroxy acid, confirmed by the reported physical constants and ir and NMR data (Table I).

α-Hydroperoxylation. Into a 100-ml round-bottom flask with side arm, provided with a magnetic stirrer, attached to the nitrogen manifold and protected with a rubber septum, were placed 50 ml of anhydrous THF, cooled to −78 °C by means of a dry ice/acetone bath, and saturated with dry oxygen gas by means of a 12G stainless steel capillary. With magnetic stirring, continuous bubbling of oxygen, and cooling at −70 °C, by means of a 12G stainless steel capillary syphon the above prepared α-lithiocarboxylate solution was added dropwise over a period of 110 min. After 30 min of stirring at −78 °C, the reaction mixture was hydrolyzed (controlling the temperature rigorously) by adding 10% aqueous HCl dropwise by means of a syringe. The reaction mixture was allowed to warm up to 5 °C, transferred to a separatory funnel, diluted with two volumes of ice, and extracted with 6 × 10 ml of ether, keeping the temperature below 10 °C by adding ice. The combined ether extracts were dried over $MgSO_4$ in the refrigerator, and the ether rotoevaporated (10°C, 10 mm) until solidified α-hydroperoxy acid **1** remained. The last traces of solvents (THF) were removed at 10 °C (0.1 mm). The peroxide content was determined by iodometric titration and the pure α-hydroperoxy acid obtained by recrystallization. The results are summarized in Table I and the experimental data for each system described below.

α-Hydroperoxyphenylacetic acid (1a) was obtained in 82% yield of crude product (by iodometry) and three times recrystallized from ether/benzene, mp 96–97 °C dec, 96% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$), 1725 (C=O), 700 cm^{-1} (monosubstituted aromatic); NMR (60 MHz, $CDCl_3$) δ (Me_4Si) 5.53 (1 H, s, α-H), 6.82 (2 H, s, –OOH and $-CO_2H$, broad), and 7.44 (5 H, m, C_6H_5, broad).

α-Hydroperoxydiphenylacetic acid (1b) was obtained in 67% yield of crude product (by iodometry) and three times recrystallized from ether–benzene, mp 100–102 °C dec, 95% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$), 1725 (C=O), 700 cm^{-1} (monosubstituted aromatic); NMR (60 MHz, $CDCl_3$) δ (Me_4Si) 7.40 (10 H, m, C_6H_5, broad).

9-Hydroperoxy-9-fluorenecarboxylic acid (1c) was obtained in 66% yield of crude product (by iodometry), and recrystallized three times from ether–benzene, mp 126–128 °C dec, 92% iodometric titer. The spectral data follow: ir (KBr) 3500–2800 (–OOH and $-CO_2H$) and 1720 cm^{-1} (C=O); NMR (60 MHz, CD_3COCD_3) δ (Me_4Si) 6.00 (2 H, s, –OOH and $-CO_2H$, broad) and 7.40 (8 H, m, aromatic CH, broad).

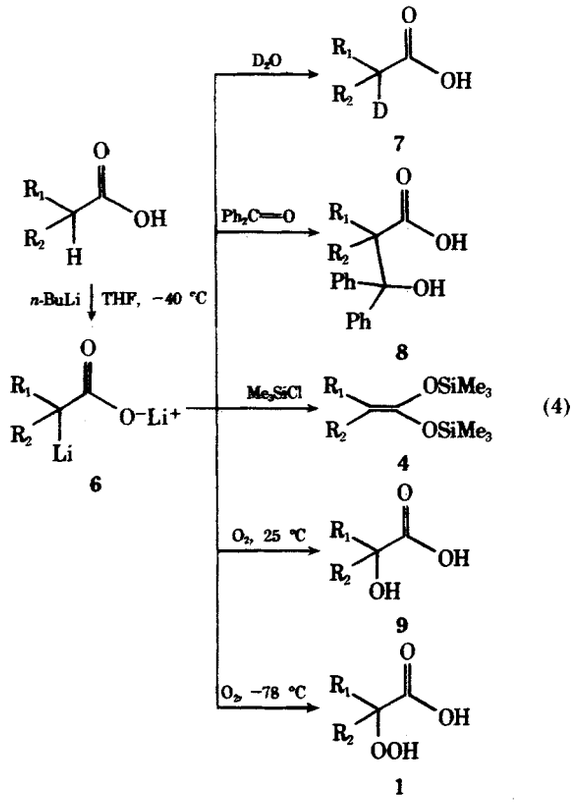
Discussion

The results of Table I clearly reveal that essentially quantitative α-lithiation of arylacetic acids with *n*-BuLi is feasible. In fact, we have used this process as a convenient method for titration of alkyllithiums. However, the end point is not sharp and the titer is at best within 5% reliable.[12]

For nonaromatic acids only fair results are obtained. Even under the optimized conditions of Table I, due to the reduced acidity of the α hydrogen, substantial carbonyl attack by the alkyllithium takes place, affording the respective alkyl ketones. For example, at lower temperatures (−78 °C) very little reaction, i.e., neither α-lithiation nor carbonyl addition, was observed since the acid was recovered unchanged in high yield. At higher temperatures (0 °C) an increased amount of carbonyl addition was observed. The use of *tert*-butyllithium did

not improve the yield of α-lithiation; on the contrary, more carbonyl addition took place.

The various electrophilic substitution processes are summarized in eq 4. Deuterium oxide and trimethylsilyl chloride



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are excellent electrophiles for titrating the α-lithiocarboxylates. On the basis of NMR data, essentially quantitative deuteration and trimethylsilylation takes place. Since both are hard electrophiles, the attack takes place on oxygen rather than carbon and steric factors are minimized. For example, the significance of steric factors is dramatically exposed in the reaction of the α-lithiocarboxylates with benzophenone. Not even traces of the α-hydroxy acids **8b** and **8c** could be detected and only low yields of **8d** and **8e** could be isolated. Hydroxymethylation with ketones or aldehydes is not recommended for the titration of α-lithiocarboxylates.

Molecular oxygen, a soft electrophile, as expected affords high yields of the desired α-hydroxy and α-hydroperoxy acids, depending on the reaction conditions. Since the oxygen molecule is a relatively small electrophile, α-attack is unobstructed. Although this direct α-peroxylation of α-lithiocarboxylates is a convenient and efficient preparation of α-hydroperoxy acids derived from arylacetic acids, great care must be exercised in their isolation in view of their labile nature toward thermal, acid-, and base-catalyzed decarboxylation. Presently we are extending this method to other hitherto unavailable α-hydroperoxy acids which are of interest in biological oxidations.

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Registry No.—**1a**, 60538-67-2; **1b**, 60538-68-3; **1c**, 60538-69-4; **6a**, 60538-70-7; **6b**, 60538-71-8; **6c**, 60538-72-9; benzeneacetic acid, 103-82-2; α-phenylbenzeneacetic acid, 117-34-0; 9*H*-fluorene-9-carboxylic acid, 1989-33-9; *n*-butyllithium, 109-72-8.

References and Notes

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Chemiluminescence from Base-Catalyzed Decomposition of α-Hydroperoxy Esters. Dioxetanone Mechanism[1]

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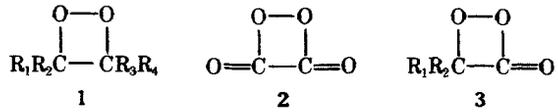
Chemiluminescence (CL) was observed from the methoxide-catalyzed decomposition of six α-hydroperoxy esters **4a–f** in the presence of fluorescein in MeOH. The quantum yields (Φ) of the CL were in the range of 5×10^{-6} to 3×10^{-4} and increased linearly with increasing concentration of fluorescein. Although the decomposition of **4** was dramatically accelerated by addition of water, the CL intensity remained constant, and hence Φ was significantly reduced. This suggests that the major reaction is the hydrolytic decomposition and the CL comes from a minor reaction involving no HO^- ion. The efficiency of fluorescers was in the order of fluorescein ≃ eosin ≫ diphenylanthracene > dibromoanthracene. These results were discussed in connection with a mechanism of CL involving a charge-transfer complex between dioxetanone (**3**) and fluorescers. This mechanism differs from the reported CL from the spontaneous decomposition of **3** producing a triplet ketone.

1,2-Dioxetanes (**1**)[2] and 1,2-dioxetanedione (**2**)[3] are well known as intermediates or potent starting materials for chemiluminescence. 1,2-Dioxetanones (**3**) were synthesized[4b] from α-hydroperoxy acids and shown to be luminescent.[4–6]



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