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Multigram Synthesis of a Combustion-Relevant δ-Ketohydroperoxide through Sulfonylhydrazine Substitution

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Abstract: A synthesis of a δ-ketohydroperoxide is described, addressing potential functional-group compatibilities in these elusive species relevant to combustion and atmospheric chemistries. The hydroperoxide is installed via sulfonylhydrazine substitution, which was found to be more effective than displacement of secondary halides. As part of this protocol, it was observed that 1,2-dimethoxyethane is an advantageous medium for the reaction, avoiding the formation of a tetrahydrofuran hydroperoxide side product. This discovery facilitated the multigram synthesis (6 steps, 41 % yield overall) and discrete characterization of the target δ-ketohydroperoxide.

Introduction

Organic peroxides and their related radicals are highly relevant species in the combustion and atmospheric chemistry disciplines.[1] Arising from the addition of molecular oxygen to carbon-centered radicals, the formation of peroxy radicals (ROO•) initiates a degenerate chain-branching sequence that drives combustion. The process is quite complex, with multiple isomers produced from a single hydrocarbon radical. For example, intramolecular H-abstraction by ROO• produces a carbon-centered radical (•QOOH), which leads to numerous cyclic ether isomers via unimolecular decomposition depending on the proximity of the unpaired electron to the –OOH group. In addition to unimolecular reactions, bimolecular reactions of •QOOH occur with O_2 and subsequently lead to ketohydroperoxide isomers that provide the chain-branching step at low temperatures.[1a,b] Similar radical mechanisms are also relevant in atmospheric chemistry, where ketohydroperoxides are direct oxidation products of organic molecules and are central to autoxidation and to aerosol formation.[1e,2]

Ketohydroperoxides (KHPs) are a class of closed-shell intermediates distinct by the proximity of the hydroperoxy group to the carbonyl group.[1c] Both the existence of these two functional groups and their relative positioning on a given molecule are expected to influence the selectivity of that molecule toward reaction pathways. Despite the importance of KHP reaction mechanisms,[1d,3] direct chemical kinetics studies on KHP molecule reactivity are nonexistent, and even isolated molecules featuring both a ketone and hydroperoxide are decidedly rare.[4] Synthesis of the putative intermediates as defined single components will enable direct, comprehensive profiling in chemical kinetics studies with KHP as the initial reactant rather than the detected product. In turn, such studies may promote important developments in chemical kinetics theory and modeling[5] that are critical for enhancing combustion efficiency and energy sustainability.[6]

From a synthetic chemistry perspective, organic hydroperoxides hold a rather unique position. There have been a handful of methods for the synthesis of hydroperoxides from various precursors,[7] but compared to many other functional groups, peroxides are relatively understudied. Consequentially, the installation of hydroperoxides in the presence of other functional groups, addressing both compatibility and their positional relationships, has not been thoroughly addressed. Given the increased relevance of organic peroxides as medicinally active agents,[8] the development of reliable synthetic transformations of hydroperoxides becomes more imperative.

The interreactivity between ketones and hydroperoxides is particularly complex.[9,10] A ketohydroperoxide species may easily close to the corresponding endoperoxide hemiacetal, which may complicate its synthesis, stability profile, and manipulation. Hydroperoxides-more readily than alcohols-will also form (hemi)peroxyacetals with ketones in *inter*molecular processes, further increasing the complexity of their syntheses. An example by Milas from 1939 shows the simple combination of cyclopentanone and hydrogen peroxide leading to multiple

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organic peroxides, illustrated in Figure 1.[11] These potential issues should impact the synthetic approach to KHP targets, dictating installation method, sequence of steps, and potential protecting group scheme. Herein, we report our synthesis and characterization of δ-KHP **1**, a representative ketohydroperoxide that addresses some of these considerations. The synthesis allows for access of multigram quantities of δ-KHP **1**, one of the isomers likely produced during cyclohexane combustion.[12,13] As part of this synthesis, we also describe an improved procedure of hydroperoxide synthesis from alkyl sulfonylhydrazines.

There were aspects of our synthetic strategy that we believed were critical to consider. Because of concerns about stability and compatibility, we wanted to implement a strategy that minimized manipulation once both functional groups were present. We expected the hydroperoxide to be quite prone to undesired transformations: the aforementioned acetalization could be promoted by mild acid or even neutral conditions, and base-mediated eliminations were conceivable. Thus, our strategy was predicated on executing minimal transformations with this group exposed. Considering the ease of using H_2O_2 as a peroxide source, nucleophilic substitution reactions with different leaving groups appeared to be a reasonable starting point for hydroperoxide installation. The resulting hydroperoxide would be promptly protected.[14] How to manage the ketone was unclear. Ketones may be susceptible to nucleophiles/bases, but protection would introduce additional steps. Moreover, protected ketones typically require acidic-type conditions for deprotection that may threaten the peroxide stability, although protecting groups with orthogonal conditions for deprotection could be considered. We therefore arrived at a net strategy outlined in Figure 2. We would use a compound bearing a secondary halide or equivalent to install the hydroperoxide, with or without the ketone moiety protected. If the ketone needed to be protected, manipulations of the protecting groups would afford the penultimate compound, which we would subject to rigorous purification. A final clean deprotection of the hydroperoxide, with minimal subsequent manipulations, would yield our target δ-KHP **1**.

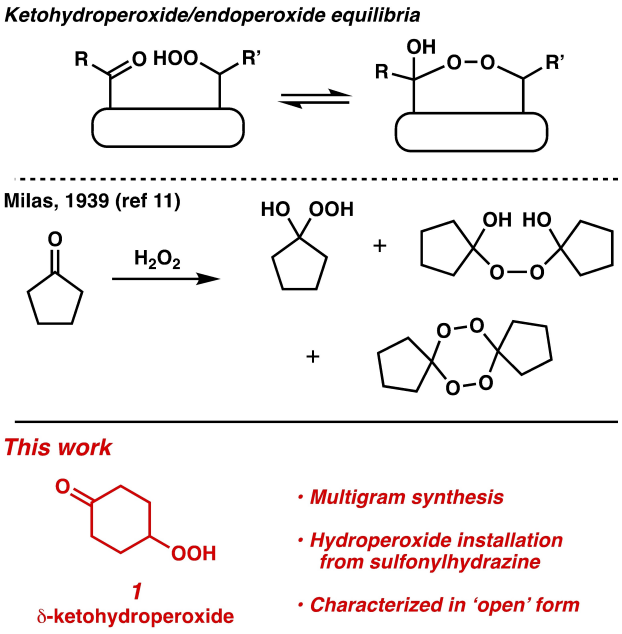


Figure 1. Synthetic facets of ketone hydroperoxide molecules.

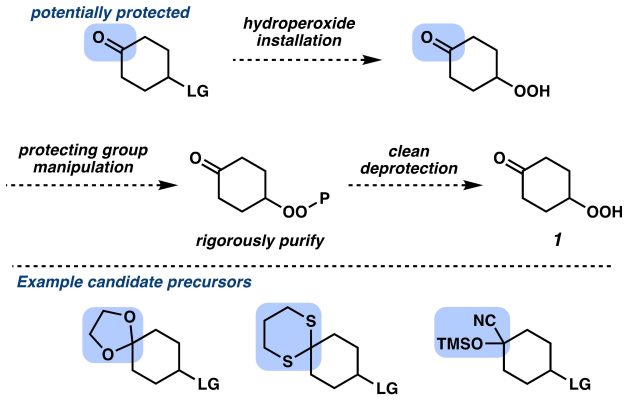
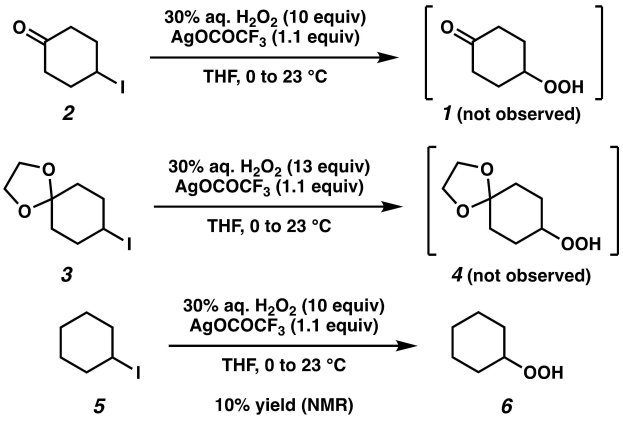


Figure 2. Synthetic plan for ketohydroperoxide **1**.

Results and Discussion

We started by evaluating 4-iodocyclohexanone (Scheme 1). Nucleophilic substitution of halides with H_2O_2 mediated by silver salts has been a frequently used method for secondary hydroperoxide synthesis.[15–17] Substitution in cyclic cases has been achieved; Mascharak and coworkers showed that iodocyclohexane was converted to cyclohexyl hydroperoxide in 23% yield using 2 equiv. H_2O_2 and 1 equiv. $AgOCOCF_3$ in dichloromethane. Ketone compatibility using this technique was a concern, though. Kharasch and Sosnovsky reported that H_2O_2 preferentially reacted with the ketone moiety in 2-chloro- and 2-bromocyclohexanone to afford the 2-halo-1-hydroperoxycyclohexan-1-ols under aqueous conditions.[18] To our knowledge, however, the silver-based methods had not been examined on substrates featuring ketones. Unfortunately, the secondary hydroperoxide was not formed using 4-iodocyclohexanone

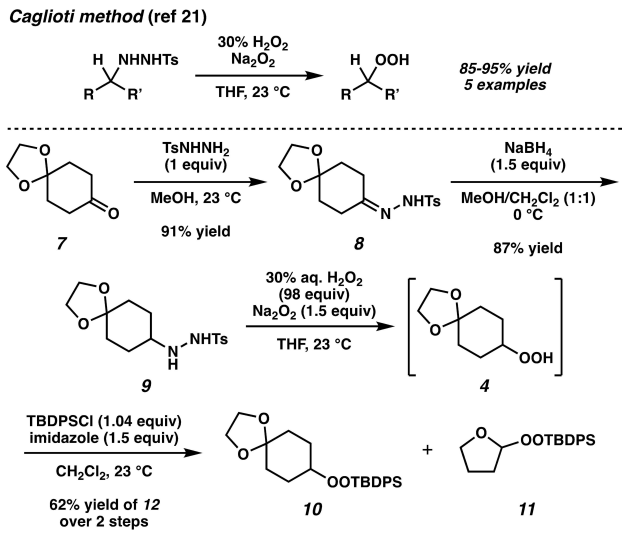


Scheme 1. Hydroperoxide synthesis via halide substitution.

(**2**).[19] The protected ketal variant (**3**) was also ineffective. Iodocyclohexane was at least modestly reactive under these identical conditions, implicating that the ketone/ketal functional group was incompatible.[20] Although there may be a solution to a ketone equivalent that would engage in this reactivity, it appeared this method was not going to be immediately fruitful toward our target. We decided to pursue a different direction.

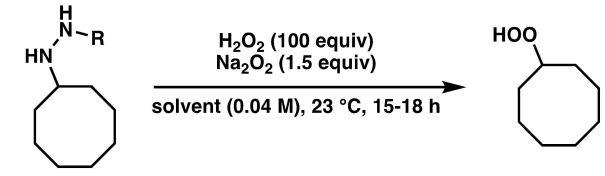
We hypothesized we needed a more active leaving group for efficient substitution at the secondary carbon. In a study by Caglioti and coworkers,[21] alkyl sulfonylhydrazines were directly converted to the corresponding alkyl hydroperoxides in excellent yields by the action of H_2O_2 and Na_2O_2 (Scheme 2). An alkyl diazonium intermediate accessed via in situ oxidation allows the high-yielding nucleophilic displacement.[22] We believed this strategy may provide a pathway for the direct multigram synthesis of our secondary alkyl peroxide; Caglioti reported secondary hydroperoxides were obtained in 85–95% yields for the five substrates evaluated. With the aforementioned considerations regarding the reactivity of the ketone functional group and to accommodate hydrazine synthesis, we opted to have the ketone again protected as the dioxolane. Thus, starting with commercially available ketone **7**, condensation with *p*-toluenesulfonyl hydrazide afforded hydrazone **8** in 91% yield. $NaBH_4$ reduction provided the sulfonylhydrazine (**9**) in excellent yield for testing the hydroperoxide synthesis method. To our delight, treatment of sulfonylhydrazine **9** with the conditions reported by Caglioti (~100 equiv. 30% H_2O_2, 1.5 equiv. Na_2O_2, THF, 23 °C) produced the desired hydroperoxide. This crude hydroperoxide was directly protected with TBDPSCl and imidazole to yield silyl peroxide **10** in 62% yield. We noted, however, the existence of silylated hydroperoxide **11**, which frequently complicated chromatographic purification.

Although this method proved viable for accessing the target secondary hydroperoxide, we believed this method warranted a closer investigation. We ultimately desired a multigram synthesis, and it was essential to have simple protocols with straightforward purifications. The THF silylperoxide side product (**11**), which was undoubtedly arising from the sulfonylhydrazine substitution step, was critical to avoid. Further, an examination of the literature[23] showed a consistent discrepancy in the hydroperoxide yields reported by Caglioti vs. the hydroperoxide yields reported by others using this protocol, perhaps also due to complications from this side product formation.[24] As a model, we evaluated this procedure using cyclooctyl tosylhydrazine (Table 1).[25] Performing the reaction under an argon atmosphere with BHT as a radical inhibitor was not beneficial to yield (entry 2). Therefore, ethereal solvents with varying miscibility with H_2O were analyzed (entries 3–6); it was expected the more miscible solvents would perform better due to homogeneous mixing with the aqueous H_2O_2. Among these solvents, only 1,2-dimethoxyethane (DME) provided similar yields to THF, while other solvents were inferior. Moving forward with DME as the solvent, the source of hydroperoxide was analyzed. Higher concentrations of aqueous hydroperoxide or urea hydroperoxide unfortunately did not improve the yield (entries 7, 8). It has been reported in an isolated case that anhydrous H_2O_2 was beneficial,[23e] but we did not observe a similar effect (entry 9). The methanesulfonyl hydrazine afforded a diminished yield (entry 10). The absence of H_2O_2 shut down the reaction completely (entry 11), while the absence of Na_2O_2 led to a significantly compromised yield (entry 12). Although we did not see an improvement in yield and reach the levels originally reported by Caglioti, in our hands the similar results between THF and DME were gratifyingly scalable (62% and 60%, respectively, equation 1).



Scheme 2. Hydroperoxide synthesis via alkyl tosylhydrazines.

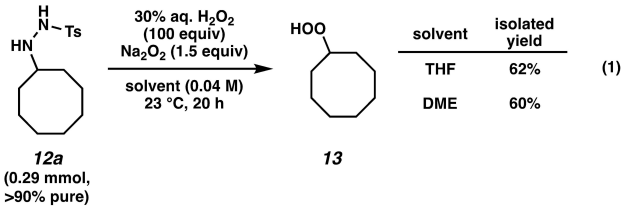
Table 1. Evaluation of hydroperoxide synthesis conditions from cyclooctyl sulfonylhydrazines.[a]



12a,b (>90% pure) **13**

entry	R	solvent	H_2O_2 source	NMR yield (%)
1	Ts (**12a**)	THF	30% aq.	56
2[b,c]	Ts	THF	30% aq.	33
3	Ts	Et_2O	30% aq.	41
4	Ts	1,4-dioxane	30% aq.	<5
5	Ts	MTBE	30% aq.	15
6	Ts	DME	30% aq.	54
7	Ts	DME	50% aq.	30
8	Ts	DME	Urea•H_2O_2	34
9	Ts	DME	Anhydrous (13.6 M in Et_2O)	42
10	Ms (**12b**)	DME	30% aq.	32
11	Ts	DME	none	0
12[d]	Ts	DME	50% aq.	24

[a] All reactions were performed on 0.034 mmol **12**. [b] Reaction was conducted under Ar. [c] 1.0 equiv. BHT added. [d] Reaction performed w/o Na_2O_2.



The comparison between using THF and DME as solvent was notable. The former has been uniformly employed for this method, but there has been no mention of the THF hydroperoxide side product. This compound can be presumably removed via chromatography in most cases, but when the transformation is performed in DME, no similar solvent peroxides were observed in the reaction mixtures (Figure 3).[26] We attribute this difference to their respective rates of α-C–H abstraction in these ethereal solvents; cyclic THF has been consistently measured to be faster in C–H abstraction than Et_2O, an analogous acyclic ether.[27] We observed suppression of the THF hydroperoxide when BHT was added (Table 1, entry 2), consistent with a radical-based origin.[28] Although the use of DME did not give an improved reaction yield, we found the use of this solvent greatly simplified purification, and this protocol was superior for our purposes. We recommend DME as the solvent of choice for those interested in using this tosylhydrazine technique.

With this improved protocol in hand, we turned our attention to the completion of the δ-KHP synthesis (Scheme 3). The same benefit of using DME was found using tosylhydrazine **9**, where the crude reaction mixture appeared significantly cleaner when using this solvent (See the Supporting Information, Figure S2). This crude hydroperoxide was again directly silylated to yield silyl peroxide **10** in 62% yield over the two steps on a 5-gram scale. This protocol provided a protected peroxide that was sufficiently robust to tolerate ketal hydrolysis. Using the palladium-catalyzed transacetalization conditions described by Lipshutz and coworkers,[29] ketone **14** was afforded in 96% yield. This ketone could then be rigorously purified in preparation for the final deprotection. For this last step, we intended to avoid acidic conditions, to at least minimize the likelihood of any ketalization processes. Fluoride-based methods thus seemed a better option, and we found that NH_4F in MeOH[30] was ideal compared to TBAF, as it avoided any complications from tetrabutylammonium contaminants in the final purification. It was straightforward to remove the *tert*-butyldiphenylsilyl byproduct via rapid chromatography, and the resulting ketohydroperoxide (**1**) was isolated in excellent yield and purity.

Although it was conceivable ketohydroperoxide **1** would readily convert to the endoperoxide ketal,[31] the compound was isolated almost exclusively in its "open" form (Figure 4). ^{1}H NMR data are consistent with other 4-oxygenated cyclohexanones (e.g., **15**, **16**);[32] the four distinct signals between 1.9 and 2.6 ppm are reflective of the methylene protons in the cyclohexanone motif. These signals are also inconsistent with the methylene proton signals in lactones **17** and **18**,[33] which would display the similar splitting patterns and coalescence of a bicyclo[2.2.2]octane structure. When ketohydroperoxide **1** was treated with $CHCl_3$, minor conversion to the presumed endoper-

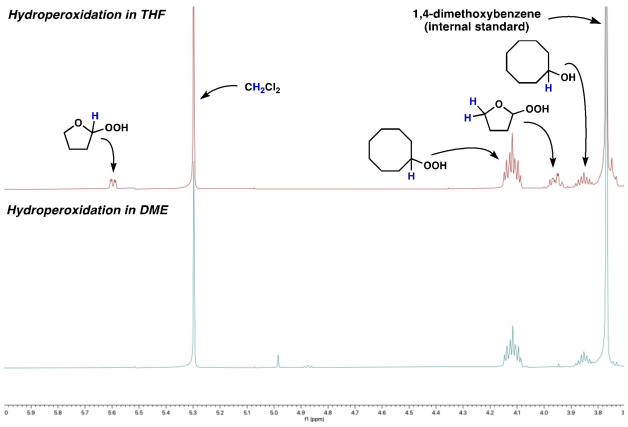
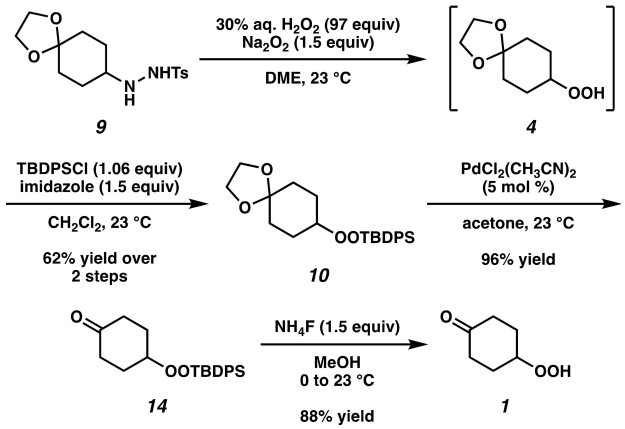


Figure 3. Crude ^{1}H NMR comparison of conditions for **12a**→**13** using THF (top) vs. DME (bottom) as solvent (400 MHz, $CDCl_3$).



Scheme 3. Completion of synthesis of ketohydroperoxide **1**.

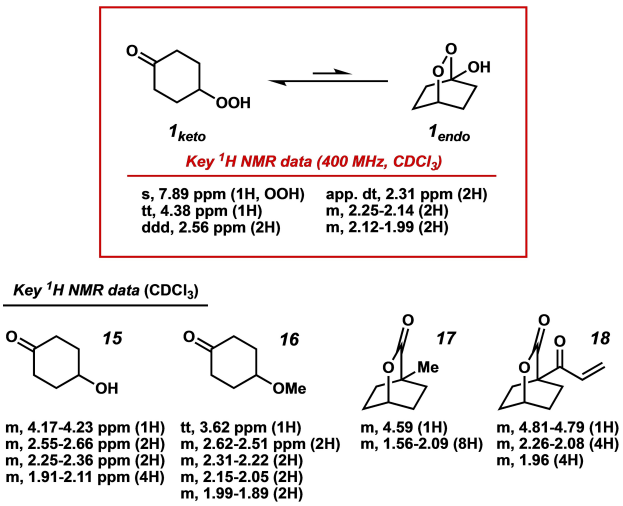


Figure 4. Ketohydroperoxide characterization: ^{1}H NMR data comparison.[32,33]

oxide was observed;[34] complex signals consistent with these lactone methylene protons were evident in the ^{1}H NMR spectrum. As a newly isolated hydroperoxide with 12% active oxygen, we measured the stability of the compound using differential scanning calorimetry. Modest heat evolution began to be observed at 92 °C, while the onset temperature and peak temperature were found to be 128 °C and 161 °C, respectively. The onset temperature for secondary hydroperoxide **1** is within a standard range reported for common tertiary hydroperoxides.[35]

Direct measurement of the photoionization spectrum of ketohydroperoxide **1** was conducted using multiplexed photoionization mass spectrometry[36] at the Advanced Light Source synchrotron.[34,37] The spectrum of ketohydroperoxide **1** was measured at an exact mass of *m/z* 130.06 ($C_6H_{10}O_3$) from 8.5–11.0 eV and is compared in Figure 5 to the ion signal at *m/z* 130 from cyclohexane combustion.[12,38] The overlap of the two spectra indicates that ketohydroperoxide **1** may comprise a significant fraction of the possible isomers of KHP derived from cyclohexane.

Conclusion

We have successfully synthesized a unique ketohydroperoxide compound with scalability that can provide sufficient material for subsequent combustion studies of cyclohexane. The synthesis features the conversion of an alkyl tosylhydrazine to the corresponding alkyl peroxide, where we found that DME was a valuable solvent for streamlining purification and affording a cleaner hydroperoxide product. Specific protecting-group manipulations were determined to allow facile transformations and realize the full synthesis. We anticipate that this strategy can inform future synthetic approaches to peroxide compounds featuring multiple functional groups, particularly ketones and related carbonyls. Current efforts are directed toward syntheses of other ketohydroperoxides and studies of their respective reactivities in combustion processes. Results will be reported in due course.

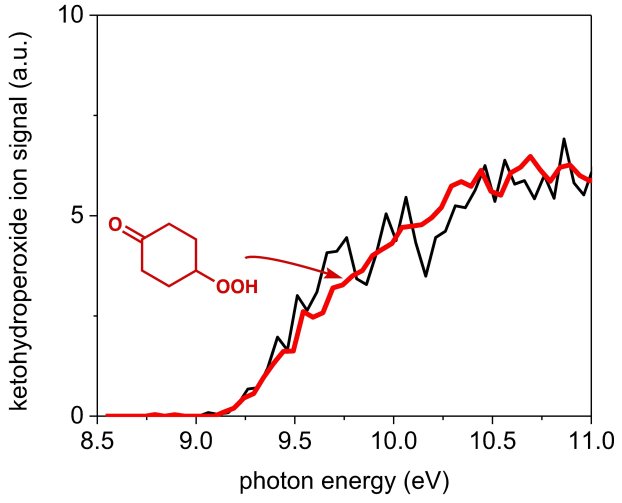


Figure 5. Ketohydroperoxide characterization: photoionization spectra overlay of *m/z* 130 signal from cyclohexane oxidation (black) and authentic ketohydroperoxide **1** (red).

Experimental Section

General Information: Reactions were performed under an argon atmosphere unless otherwise noted. Dichloromethane was purified by passing through an activated alumina column. All other solvents and reagents were used as received unless otherwise noted. Commercially available chemicals and reagents were purchased from Alfa Aesar (Ward Hill, MA), MilliporeSigma (St. Louis, MO), Oakwood Products (West Columbia, SC), and Acros Organics (Geel, Belgium). 30% aq. H_2O_2 solution was purchased from Fisher Scientific (Waltham, MA). 50% aq. H_2O_2 solution was purchased from MilliporeSigma (St. Louis, MO). Qualitative TLC analysis was performed on 250 mm thick, 60 Å, glass backed, F254 silica (SiliCycle, Quebec City, Canada). Visualization was accomplished with UV light and/or exposure to *p*-anisaldehyde or $KMnO_4$ stain solutions followed by heating. Flash chromatography was performed using SiliCycle silica gel (230–400 mesh). ^{1}H NMR spectra were acquired on a Varian Mercury Plus NMR (at 400 MHz) and are reported relative to $SiMe_4$ (δ 0.00). ^{13}C NMR spectra were acquired on a Varian Mercury Plus NMR (at 100 MHz) and are reported relative to $SiMe_4$ (δ 0.0). All IR spectra were obtained as thin films with a Nicolet iS-100 FTIR and are reported in wavenumbers (ν). High resolution mass spectrometry (HRMS) data were acquired via electrospray ionization (ESI) using either a ThermoFisher Orbitrap Q-Exactive or a ThermoFisher Orbitrap Elite, the latter at the Proteomics and Mass Spectrometry Facility at the University of Georgia.

Hazard statement: Although no safety issues were encountered in the course of this work, any preparative work with peroxides should be performed with an appropriate awareness for the potential hazards arising from spontaneous and exothermic decomposition.[39] Use of appropriate personal protective equipment and engineering controls are encouraged.

Hydrazone 8: To a solution of *p*-toluenesulfonyl hydrazide (29.8 g, 0.160 mol) in MeOH (320 mL) at 23 °C was added 1,4-cyclohexanedione monoethylene acetal (25.0 g, 0.160 mol). The resulting mixture was stirred for 1 h, after which a precipitate was present. The precipitate was collected by filtration and rinsed with hexanes (3×100 mL) to afford hydrazone **8** (47.0 g, 91% yield) as a white solid. Spectroscopic data were in agreement with those previously reported.[40] R_f: 0.17 (2:1 hexanes/EtOAc, anisaldehyde stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J=8.2 Hz, 2H), 7.73 (br. s, 1H), 7.30 (d, J=8.2 Hz, 2H), 3.94 (app. s, 4H), 2.46–2.34 (comp. m, 4H), 2.42 (s, 3H), 1.75 (app. dt, J=16.4, 6.8 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 144.2, 135.4, 129.7, 128.2, 107.7, 64.7, 34.4, 33.1, 32.1, 23.7, 21.8. IR (film): 3159, 2052, 2926, 1325, 1168 cm^{-1}. HRMS (ESI+): *m/z* calcd for $(M+Na)^+$ $[C_{15}H_{20}N_2O_4S+Na]^+$: 347.1036, found 347.1023.

Hydrazine 9: To a solution of hydrazone **8** (10.0 g, 30.8 mmol) in a 1:1 mixture of CH_2Cl_2/MeOH (122 mL) at 0 °C was added $NaBH_4$ (1.74 g, 45.9 mmol) in 3 portions over 15 min. The resulting mixture was stirred at 0 °C for 1 h. Sat. aq. NH_4Cl (100 mL) was added, and the volatile solvents were removed by rotary evaporation. The resulting mixture was then extracted with CH_2Cl_2 (5×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (2:1 hexane/EtOAc eluent) to afford hydrazine **9** (8.75 g, 87% yield) as a white solid. R_f: 0.17 (2:1 hexanes/EtOAc, anisaldehyde stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 6.07 (br. s, 1H), 3.89 (app. s, 4H), 3.03 (br. s, 1H), 2.76 (tt, J=8.8,

3.5 Hz, 1H), 2.42 (s, 3H), 1.70 (ddd, J = 17.0, 6.6, 3.3 Hz, 4H), 1.48–1.29 (comp. m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 135.6, 129.8, 128.3, 108.6, 64.44, 64.39, 56.3, 32.2, 27.9, 21.7. IR (film): 3238, 2948, 2883, 1327, 1160 cm^{-1}. HRMS (ESI+): *m/z* calcd for $(M+H)^+$ $[C_{15}H_{22}N_2O_4S+H]^+$: 327.1373, found 327.1362.

Silyl peroxide 10: To a solution of hydrazine **9** (5.00 g, 15.3 mmol) in 1,2-dimethoxyethane (380 mL) and 30% aq. H_2O_2 (152 mL, 1490 mmol) at 23 °C open to air was added Na_2O_2 (1.80 g, 23.1 mmol). The resulting mixture was stirred at 23 °C for 18 h. Aq. KH_2PO_4 buffer solution (0.05 M, 200 mL) was then added to the reaction mixture, and the volatile solvents were removed by rotary evaporation. The resulting mixture was extracted with CH_2Cl_2 (5× 300 mL). The combined organic layers were washed sequentially with H_2O (200 mL) and brine (200 mL), and then dried over $MgSO_4$ and concentrated in vacuo to afford the crude hydroperoxide (**4**, R_f: 0.33 in 2:1 hexane/EtOAc eluent, anisaldehyde stain). The crude material was then dissolved in anhydrous CH_2Cl_2 (50 mL) at 23 °C. Imidazole (1.60 g, 23.5 mmol) was then added to the reaction flask, and the resulting mixture was stirred 10 min to fully dissolve the imidazole. TBDPSCl (4.20 mL, 16.2 mmol) was then added dropwise over 2 min, and the resulting mixture was stirred for 1 h. The reaction mixture was poured into H_2O (100 mL) and extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were washed sequentially with H_2O (30 mL) and brine (30 mL), and then dried over Na_2SO_4 and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 hexane/EtOAc eluent) to afford silyl peroxide **10** (3.90 g, 62% yield over 2 steps) as a colorless oil. R_f: 0.34 (9:1 hexanes/EtOAc, anisaldehyde stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (dd, J = 7.9, 1.4 Hz, 4H), 7.43 (app. t, J = 7.2 Hz, 2H), 7.37 (app. t, J = 7.2 Hz, 4H), 4.00 (tt, J = 6.0, 4.0 Hz, 1H), 3.92 (app. t, J = 2.8 Hz, 4H), 1.88–1.76 (comp. m, 4H), 1.76–1.67 (m, 2H), 1.53–1.43 (m, 2H), 1.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.8, 133.2, 129.9, 127.7, 108.7, 80.6, 64.4, 31.2, 27.6, 27.0, 19.6. IR (film): 2994, 2857, 2359, 2341, 1275, 1105 cm^{-1}. HRMS (ESI+): *m/z* calcd for $(M+Na)^+$ $[C_{24}H_{32}O_4Si+Na]^+$: 435.1962, found 435.1947.

Ketone 14: Acetal deprotection was performed according to the protocol of Lipshutz and coworkers.[29] To a solution of silyl peroxide **10** (500 mg, 1.21 mmol) in acetone (121 mL) at 23 °C was added $PdCl_2(CH_3CN)_2$ (15.7 mg, 0.0606 mmol). The resulting mixture was stirred for 18 h. The reaction mixture was then concentrated in vacuo, and the residue was dissolved in Et_2O (50 mL). The resulting solution was washed sequentially with aq. Sat. $NaHCO_3$ (80 mL) and brine (80 mL), and then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was purified by flash chromatography (9:1 hexane/EtOAc eluent) to afford ketone **14** (429 mg, 96% yield) as a colorless oil. R_f: 0.33 (9:1 hexanes/EtOAc, anisaldehyde stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, J = 8.2, 1.2 Hz, 4H), 7.45 (app. t, J = 7.2 Hz, 2H), 7.38 (app. t, J = 7.2 Hz, 4H), 4.25 (tt, J = 5.2, 3.2 Hz, 1H), 2.44–2.31 (m, 2H), 2.15 (app. ddd, J = 10.8, 8.8, 5.0 Hz, 4H), 1.89 (app. ddd, J = 15.4, 7.2, 3.6 Hz, 2H), 1.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2, 135.8, 132.7, 130.2, 127.8, 78.6, 37.0, 28.7, 27.5, 19.6. IR (film): 2930, 2857, 1716, 1428, 1114 cm^{-1}. HRMS (ESI+): *m/z* calcd for $(M+Na)^+$ $[C_{22}H_{28}O_3Si+Na]^+$: 391.1700, found 391.1687.

Hydroperoxide 1: Three identical reactions were set up concurrently. In each, to a solution of ketone **14** (1.00 g, 2.71 mmol) in MeOH (11.0 mL) at 0 °C in a plastic vial was added NH_4F (151 mg, 4.07 mmol). The reaction mixtures were stirred for 15 min, and then warmed to 23 °C and stirred for 1 h. Upon completion, silica gel (~ 1 g) was added to the mixtures. The reaction mixtures were concentrated in vacuo. The crude residues were combined and promptly loaded on the column for flash column chromatography purification (2:1 hexane/EtOAc eluent) to afford hydroperoxide **1** (942 mg, 89% yield) as a colorless oil. R_f: 0.17 (2:1 hexanes/EtOAc, anisaldehyde stain). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 4.38 (tt, J = 5.6, 3.3 Hz, 1H), 2.56 (ddd, J = 15.4, 10.2, 5.1 Hz, 2H), 2.31 (app. dt, J = 15.2, 6.0 Hz, 2H), 2.25-2.14 (m, 2H), 2.12–1.99 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.7, 78.5, 36.9, 28.6. IR (film): 3299 (br), 3090, 3056, 1702, 1482 cm^{-1}. HRMS (ESI+): *m/z* calcd for $(M+H)^+$ $[C_6H_{10}O_3+H]^+$: 131.0703, found 131.0703.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: ketohydroperoxide · ketones · peroxides · substitution · sulfonylhydrazines

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