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# A New Peroxide Fragmentation: Efficient Chemical Generation of $^1O_2$ in Organic Media

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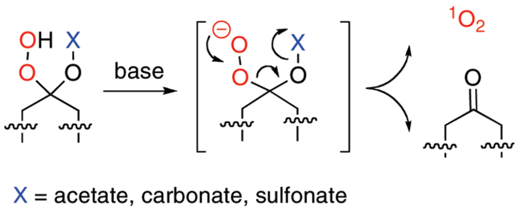
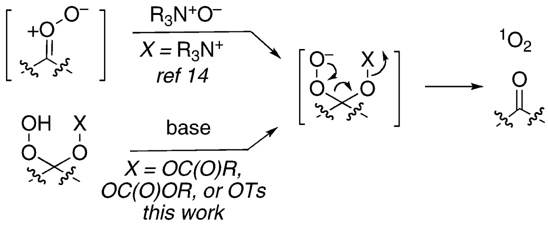
## ABSTRACT



**Monoactivated derivatives of 1,1-dihydroperoxides undergo an unprecedented base-promoted fragmentation to efficiently generate singlet oxygen ($^1O_2$) in anhydrous organic solvents.**

Singlet molecular oxygen ($^1O_2$), an important oxidant in chemistry, biology, and medicine,[1a,b] is most commonly generated via photosensitized excitation of ground-state ($^3O_2$) dioxygen.[1b,2] The discovery that $^1O_2$ is also produced from reaction of $H_2O_2$ and HOCl led to the discovery of a number of additional methods for chemical generation.[1a,3,4] However, many of these "dark" oxygenations have significant limitations. Due to the short half-life of $^1O_2$ in aqueous media,[5] methods based upon reaction of $H_2O_2$ with hypohalites,[3] alkaline earth metals,[6] transition metals,[7] lanthanides,[8] or metalloenzymes[9] must typically employ biphasic or emulsion conditions for preparative oxidations.[10] Thermal generation of $^1O_2$ from phosphite ozonides,[11] silyl hydrotrioxides,[12] or arene endoperoxides[13] can be conducted in organic solvents but requires preparation of unstable precursors. We report an efficient and convenient generation of $^1O_2$ in organic solvents via an unprecedented fragmentation of derivatives of 1,1-dihydroperoxides (Scheme 1).

**Scheme 1.** Fragmentation of Peroxyacetals



Our discovery stemmed from earlier research on "reductive" ozonolysis, in which the presence of amine *N*-oxides

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[1] (a) Foote, C. S.; Clennan, E. L. In *Active Oxygen in Chemistry*; Foote, C. S., Valentine, J. S., Greenberg, A., Liebman, J. F., Eds.; Blackie Academic and Professional: London, 1995; pp 105. (b) Clennan, E.; Pace, A. *Tetrahedron* **2005**, *61*, 6665.

[2] Schmidt, R. *Photochem. Photobiol.* **2006**, *82*, 1161.

[3] Foote, C. S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* **1968**, *90*, 975–8. Greer, A. *Acc. Chem. Res.* **2006**, *39*, 797.

[4] Adam, W.; Kazakov, D. V.; Kazakov, V. P. *Chem. Rev.* **2005**, *105*, 337.

[5] Wahlen, J.; De Vos, D. E.; Jacobs, P. A.; Alsters, P. L. *Adv. Synth. Catal.* **2004**, *346*, 152. The half-life of $1O_2$ ranges from 1−2 $\mu$s in $H_2O$ to 60 $\mu$s in $CH_3CN$ to nearly ms in perhalogenated solvents. See: Wilkinson, F.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data* **1995**, *24*, 663.

[6] Pierlot, C.; Nardello, V.; Schrive, J.; Mabille, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem.* **2002**, *67*, 2418.

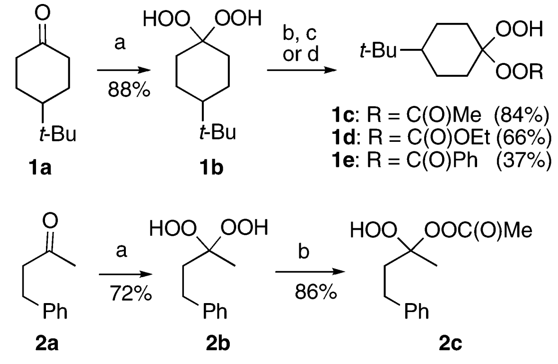
[7] Sels, B. F.; De Vos, D. E.; Jacobs, P. E. *J. Am. Chem. Soc.* **2007**, *129*, 691. Caron, L.; Nardello, V.; Alsters, P. L.; Aubry, J.-M. *J. Mol. Cat., A* **2006**, *251*, 194.

10.1021/ol9018216 CCC: $40.75

was found to promote direct ozonolytic conversion of alkenes to aldehydes and ketones.[14] The proposed mechanism, involving formation and fragmentation of a zwitterionic peroxy/oxyammonium acetal, also predicted stoichometric generation of $^1O_2$ (Scheme 1). However, this prediction could not be easily tested within an ozonolysis reaction. In search of more accessible precursors for the putative fragmentation, we discovered that readily available derivatives of 1,1-dihydroperoxides will generate $^1O_2$ under preparatively useful conditions.

The precursor 1,1-dihydroperoxides are readily available and possess surprising kinetic stability.[15,16] The dihydroperoxides of 4-*tert*-butylcyclohexanone and 4-phenyl-2-butanone, **1b** and **2b**, respectively, were prepared in high yield by $Re_2O_7$-catalyzed reaction of the ketones with aq $H_2O_2$ (Scheme 2).[17] Monoperesters (**1c**, **1e**, **2c**) and a monopercarbonate (**1d**) were prepared by acylation or carboxylation of the dihydroperoxides.[18] The monoesters were stable for several days at room temperature or weeks at −20 °C.[19] In contrast, monopercarbonate **1d** could be isolated and purified but underwent slow ring-exansion to 4-*tert*-butylcaprolactone even at room temperature.[20]

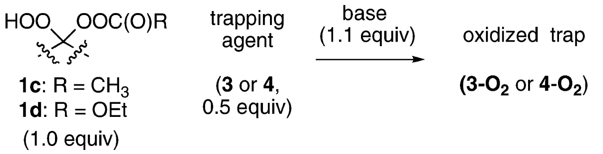
**Scheme 2.** Preparation of Peroxide Substrates[a]



[a] Key: (a) ref 17; (b) $Ac_2O$, DMAP; (c) EtOC(O)Cl, pyr; (d) BzCl, pyr.

Addition of KOtBu to a THF solution of **1c** resulted in immediate bubbling, accompanied by disappearance of starting material and formation (TLC) of 4-*tert*-butylcyclohexanone. Encouraged by this observation, we repeated the reaction in the presence of $^1O_2$ trapping reagents (Table 1 and Figure 1).[1a] Addition of KOtBu to a THF solution of **1c** and terpinene (**3**) resulted in formation of ketone **1a** (TLC) and endoperoxide **3-O₂**.[21] A similar result was obtained with percarbonate **1d**. An increased yield of $^1O_2$ from **1c** was observed at lower temperature, in acetonitrile (MeCN), or in the presence of diphenylisobenzofuran (DPBF, **4**), a more reactive trap which was completely consumed whether present in 0.5 or 0.75 equiv relative to the monoperester.[22] Efficient $^1O_2$ generation was also observed from reaction of

**Table 1.** Generation of $^1O_2$ from **1c** and **1d**[a]



| reagents | | base | solvent | time (h) | $T$ (°C) | product | yield[b] (%) |
|---|---|---|---|---|---|---|---|
| **1c** | **3** | KOtBu[c] | THF | 1 | 0 | **3-O₂** | 15 |
| **1c** | **3** | KOtBu[c] | THF | 2 | −78 | **3-O₂** | 21 |
| **1c** | **3** | KOtBu | MeCN | 0.5 | 0 | **3-O₂** | 30 |
| **1c** | **4** | KOtBu | MeCN | 1 | 0 | **4-O₂** | 50 (48)[d] |
| **1c** | **4** | KOtBu | MeCN | 1 | 0 | **4-O₂** | 75[e] |
| **1d** | **3** | KOtBu | MeCN | 1 | 0 | **3-O₂** | 39 |
| **1c** | **3** | $K_2CO_3$ | MeCN | 1 | 0 | **3-O₂** | NR |
| **1c** | **3** | $Cs_2CO_3$ | MeCN | 1 | 0 | **3-O₂** | 27 |
| **1c** | **3** | KOAc | MeCN | 1 | 0 | **3-O₂** | NR |
| **1c** | **3** | TBAF | MeCN | 0.2 | 0 | **3-O₂** | 39 |

[a] Trapping agents shown in Figure 1. [b] **3-O₂** or **4-O₂** vs **1c** or **1d**. [c] **1c** or **1d** added to base except for these cases. [d] Isolated yield. [e] 0.75 equiv of **4**.

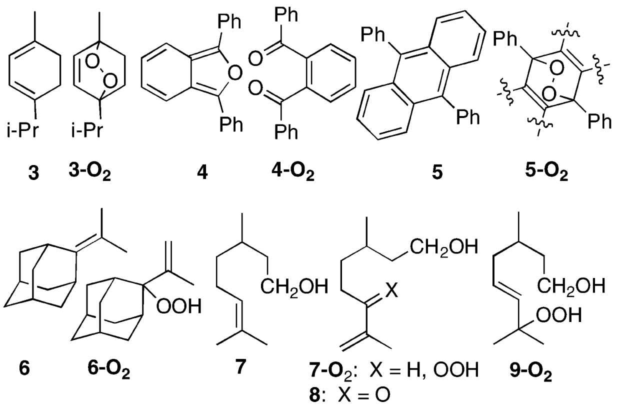


**Figure 1.** Trapping substrates and products

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(8) Nardello, V.; Barbillat, J.; Marko, J.; Witte, P. T.; Alsters, P. L; Aubry, J.-M. *Chem.—Eur. J.* **2003**, *9*, 435.

(9) Renirie, R.; Pierlot, C.; Aubry, J.-M.; Hartog, A. F.; Schoemaker, H. E.; Alsters, P. L.; Wever, R. *Adv. Synth. Catal.* **2003**, *345*, 849.

(10) See, for example: Aubry, J.-M.; Adam, W.; Alsters, P. L.; Borde, C.; Queste, S; Marko, J.; Nardello, V. *Tetrahedron* **2006**, *62*, 10753.

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(14) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Tetrahedron* **2006**, *62*, 10747.

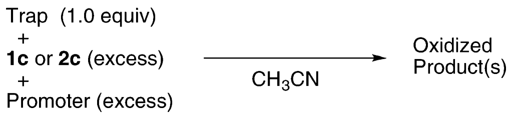
(15) Li, Y.; Hao, H.-D.; Zhang, Q.; Wu, Y. *Org. Lett.* **2009**, *11*, 1615, and references therein.

(16) Dihydroperoxide **1b** is not detonated by a hammer blow and melts without decomposition at 78−80 °C. However, even though no hazards were experienced in the course of this work, any preparative work with peroxides should be conducted with an awareness of the potential for spontaneous and exothermic decomposition reactions. See the Supporting Information for references related to safe handling of peroxides.

(17) Ghorai, P.; Dussault, P. H. *Org. Lett.* **2008**, *10*, 4577, and references therein.

monoperester **1c** with $Cs_2CO_3$, but not $K_2CO_3$ or KOAc. This disparity drew our attention to the potential importance of ion pairing, and we turned to *n*-$Bu_4NF$ (TBAF) as a convenient base which would afford a highly dissociated peroxyanion. Gratifyingly, treatment of **1c** with TBAF led to extremely rapid reaction and a 39% yield of $^1O_2$ (as **3-O₂**).

**Table 2.** Protocols for Preparative Oxidation



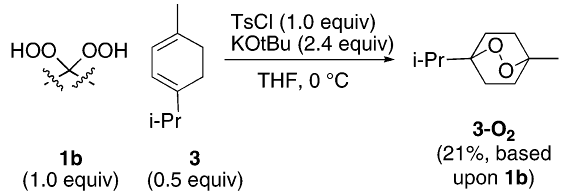
| perester (equiv) | trap | promoter[a] | time (h) | $T$ (°C) | products (yield, %)[b] |
|---|---|---|---|---|---|
| **1c** (3) | **4** | TBAF [c] | 0.5 | 0 | **4-O₂** (91) |
| **1c** (2) | **7** | TBAF[c] | 0.5 | 0 | NR |
| **1c** (4) | **3** | CsF, TMA | 0.5 | rt | **3-O₂** (69) |
| **1c** (1.5) | **4** | CsF, TMA | 0.5 | rt | **4-O₂** (94) |
| **1c** (8) | **5** | CsF, TMA | 1 | rt | **5-O₂** (81) |
| **1c** (6) | **6** | CsF, TMA | 0.5 | rt | **6-O₂** (76) |
| **1c** (8) | **7** | CsF, TMA | 0.5 | rt | **7-O₂/9-O₂/8** (91, 58:28:14) |
| **1e** (3) | **3** | CsF, TMA | 0.5 | rt | **3-O₂** (62) |
| **2c** (3) | **3** | CsF, TMA | 0.5 | rt | **3-O₂** (66) |

[a] Promoter present in 2.4 equiv relative to monoperester. [b] Based upon conversion of trap to product. [c] THF as solvent.

Further exploring the TBAF-promoted reaction (Table 2), we found that the use of excess TBAF and **1c** allowed consumption of furan **4** but failed to oxidize the less reactive **7**. Concerned that overly rapid generation of $^1O_2$ might allow escape from a saturated solution, we investigated the decomposition of excess (1.5−8 equiv) monoperester in the presence of CsF and $Me_4NOAc$ (TMA). Reactions were allowed to run for 30 min, but were typically complete (TLC) within 10 min. Complete consumption of all substrates was now observed. Citronellol (**7**) reacted to furnish a 91% yield of a 58:28:14 mixture of **7-O₂**, **9-O₂**, and ketone **8**. The formation of the isomeric hydroperoxides is characteristic for reactions of $^1O_2$ with **7**;[6,7] ketone **8** derives from base-promoted fragmentation of **7-O₂**.[23] The CsF protocol was also successfully applied to monoperesters **1e** and **2c**.

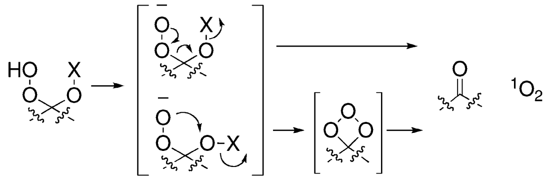
Finally, $^1O_2$ can be generated via in situ formation and decomposition of monoperoxysulfonates. Although we were unable to isolate a monoperoxysulfonate, reaction of **1b** and terpinene (**3**) with toluenesulfonyl chloride (1.0 equiv) and KOtBu resulted in the rapid disappearance (TLC) of the dihydroperoxide and the formation of **3-O₂** (Scheme 3).

**Scheme 3.** Generation of $^1O_2$ from 1,1-Dihydroperoxide



The unprecedented fragmentation described above could involve a Grob-like fragmentation[24] or, alternatively, decomposition of an unstable peroxetane derived from 4-*exo-tet* attack of the peroxyanion on the activated peroxide (Scheme 4).[25] Regardless of pathway, the fragmentation clearly requires both a highly dissociated peroxyanion and a peroxide activated toward heterolytic O−O scission. For example, the monoperesters do not generate oxygen in the absence of base, while we found the 1,1-dihydroperoxides to be unaffected by the bases employed in these studies.[26] The efficiency of $^1O_2$ production from the new fragmentation compares very favorably with known oxygen-generating systems.[4,6−8]

**Scheme 4.** Potential Mechanisms



In conclusion, we have developed a new heterolytic fragmentation that allows efficient and rapid generation of $^1O_2$ in nondeuterated organic solvents from readily available precursors. The clean regeneration of the parent ketone suggests an avenue for possible development of solid-supported or phase-separable reagents while the efficiency

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(18) Cudden, R. C. P.; Hewlett, C. *J. Chem. Soc. C* **1968**, 298. Dihydroperoxide monoesters have been investigated as radical initiators: Van de Bovenkamp-Bouwman, A. G.; Van Gendt, J. W. J.; Meijer, J.; Hogt, A. H; Van Swieten, A. P. PCT Int. Appl. WO 9932442 A1 19990701, 1999.

(19) Monoester **1c** is not detonated by a hammer blow and melts without decomposition at 37 °C. It is stable for less than 1 day at 60 °C.

(20) Percarbonates of tertiary hydroperoxides and monoperesters of 1,1-dihydroperoxides are both known to undergo Criegee rearrangement: Villenave, J. J.; Filliatre, C.; Maillard, B.; Jaouhari, R. *Bull. Soc. Chim. Belg.* **1982**, *91*, 301. Velluz, L.; Amiard, G.; Martel, J.; Warnant, J. *Compt. Rend.* **1957**, *244*, 1937 We are uncertain as to the basis for the increased stability of **1c** vs **1d**.

(21) Reported yields are based upon either isolation or quantitative GC/MS of oxidation products relative to an internal standard; see the Supporting Information for details. In general, the ketone byproduct (**1a** or **2a**) was recovered in good yield from the decomposition reactions.

(22) Due to the facility of self-sensitized oxidation, the use of DPBF for quantitative experiments should include control reactions or take care to exclude light and oxygen. See: Owakowsa, M. *J. Chem. Soc., Faraday Trans. 1* **1984**, *80*, 2119.

(23) Kornblum, N.; DelaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880.

(24) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535.

(25) Although 4-*exo/tet* displacements by peroxyanions to form dioxetanes have been observed: Kopecky, K.; Filby, J. E.; Mumford, C.; Lockwood, P. A.; Ding, J.-Y. *Can. J. Chem.* **1975**, *53*, 1103 The corresponding closure to peroxetanes is unknown. The intermediacy of peroxetanes could in principle be established by the relative fractions of $^{18}O^{16}O$ formed upon decomposition of dihydroperoxides derived from mixtures of $H^{18}O^{18}OH$ and $H^{16}O^{16}OH$. We thank one of the reviewers for this suggestion.

(26) 1,1-Dihydroperoxides have been successfully bisalkylated in the presence of $Cs_2CO_3$. Kim, H. S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357–61.

and rate of $^1O_2$ production points to potential application as a power source for chemical oxygen/iodine lasers.[27]

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**Supporting Information Available:** Experimental procedures and spectral characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9018216

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(27) Endo, M. *Russ. J. Phys. Chem. A* **2007**, *81*, 1497.