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OLEFIN OXIDATIVE CLEAVAGE AND DIOXETANE FORMATION USING TRIETHYLSILYL HYDROTRIOXIDE: APPLICATIONS TO PREPARATION OF POTENT ANTIMALARIAL 1,2,4-TRIOXANES

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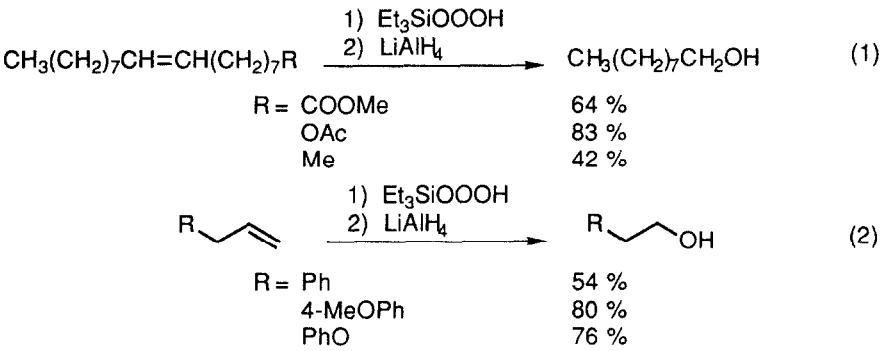
Summary: Oxidative cleavage of alkenyl esters and ethers using $Et_3SiOOOH$ was found to be easier than oxidative cleavage of hydrocarbon alkenes, and $Et_3SiOOOH$ was successfully applied to very short syntheses of new, simple, and potent antimalarial trioxanes **6** and **8**.

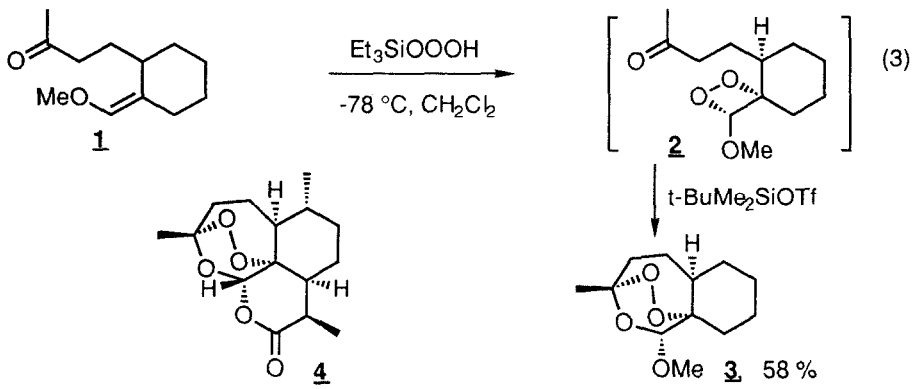
We have reported recently that triethylsilyl hydrotrioxide ($Et_3SiOOOH$), prepared *in situ* at -78°C in CH_2Cl_2 solution from triethylsilane plus ozone, is an effective new oxidizing reagent (1) that oxidatively cleaves unactivated terminal and internal alkenes into carbonyl fragments and (2) that forms 1,2-dioxetanes from vinyl aromatics and from vinyl ethers directly without the intermediacy of free $^1O_2$.[1] Now at Johns Hopkins we have discovered, and report herein, some subtle aspects of the oxidative cleavage process and some valuable applications of dioxetane intermediates produced using $Et_3SiOOOH$.

Whereas $^1O_2$ oxygen is known to react with internal disubstituted alkenes exclusively *via* an ene process,[2] excess fresh $Et_3SiOOOH$ in CH_2Cl_2 reacted completely with methyl oleate *via* an oxidative cleavage process followed by lithium aluminum hydride reduction to produce 1-nonanol and 1,9-nonanediol in 64 and 74% yields, respectively. Likewise, 1-acetoxy-9-octadecene reacted completely and gave oxidatively cleaved products in 83% yield (eq. 1). In sharp and unexpected contrast, however, the hydrocarbon 9-octadecene under identical reaction conditions reacted incompletely (40% recovered) with $Et_3SiOOOH$ and gave 1-nonanol in only 42% yield (eq. 1). A similar difference in reactivity toward $Et_3SiOOOH$ was observed between hydrocarbon 1-decene and ester ethyl 10-undecenoate. Furthermore, hydrocarbon allylbenzene reacted with excess fresh $Et_3SiOOOH$ incompletely to give 2-phenylethanol in only 54% yield, but 4-allylanisole reacted completely under identical reaction conditions to give 4-hydroxyethylanisole in 80% yield and allyloxybenzene reacted completely to give 2-phenoxyethanol in 76% yield (eq. 2). *These results indicate that the presence of an oxygen atom, even when topoligically remote from an alkene unit, facilitated oxidative cleavage of the alkene by $Et_3SiOOOH$.* Based on Plesnicar's spectroscopically established intermolecularly hydrogen-bonded dimeric structures for hydrotrioxides, [3] it is tempting to speculate that an ester or ether oxygen atom in an alkene molecule may disrupt such hydrogen-bonded dimers of $Et_3SiOOOH$ and may produce more reactive monomeric hydrotrioxides. In this context, we have found

that even one equivalent of diethyl ether or ethyl acetate did affect (albeit adversely) the oxidative cleavage of hydrocarbons allylbenzene and 9-octadecene by $Et_3SiOOOH$ in CH_2Cl_2 solution. These subtle effects of oxygen-containing alkenes and additives possibly on the structure and certainly on the chemical reactivity of hydrotrioxides are highly unusual, and therefore they deserve further study.



Jefford has shown that $^1O_2$ can be used to prepare 1,2,4-trioxane **3** from keto vinyl ether **1** in 48% yield as a structurally simplified and yet still potent version of naturally-occurring antimalarial artemisin **4**.[4] Because of the widespread incidence of malaria in certain parts of the world and because of the increasing parasite resistance to standard antimalarial drugs,[5] new and effective antimalarial compounds are needed urgently. Toward this goal, we have begun a project on synthesis of simple 1,2,4-trioxanes.[6] Using Jefford's starting keto vinyl ether **1**,[4] we have applied $Et_3SiOOOH$ to generate intermediate dioxetane **2** as indicated by 400 MHz ^1H NMR spectroscopy (singlet at δ 5.35)[4] as well as by weak chemiluminescence upon heating a very small amount of **2** on a tlc plate.[7] Treating dioxetane **2** with t-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) produced 1,2,4-trioxane **3** isolated as a single diastereomer in 58% yield (eq. 3).[8]



Formation of dioxetanes using fresh $Et_3SiOOOH$ and subsequent structural rearrangements into 1,2,4-trioxanes were applied also to other easily prepared keto vinyl ethers like **1**. For example, the *gem*-dimethylcyclohexyl system **5**, prepared from 4,4-dimethylcyclohexanone following Jefford's procedure,[4] produced trioxane **6** in 42% yield (eq. 4),[9] and benzyl vinyl ether **7**[10] gave trioxane **8** in 48% yield (eq. 5).[9] Biological *in vitro* evaluation of these trioxanes at the Walter Reed Army Insititute of Research for antimalarial activity against *P. falciparum* clones revealed some dramatic results as indicated in Table I.

Table I. Antimalarial *in vitro* Testing Against *P. falciparum* Clones

Compound	IC_{50} (D-6 African Clone)	IC_{50} (W-2 Indochina Clone)	Ratio of D-6/W-2
3	12.10	30.40	0.4
6	50.50	1.74	29
8	13.93	0.86	16
Artemisinin	1.56	0.65	2.4
Quinine	20.05	51.69	0.4
Chloroquine	3.53	30.40	0.1

Several aspects of the results in Table I are noteworthy. First, synthetic trioxanes **6** and especially **8** are similar to natural and clinically useful artemisinin in antimalarial activity in the W-2 Indochina clone. Second, synthetic trioxane **8** has 60 times higher antimalarial activity than quinine in the W-2 Indochina clone. Third, both synthetic trioxanes **6** and **8** showed a pattern of antimalarial activity completely different from that of quinine and chloroquine, with higher activity in the W-2 clone *vs.* the D-6 clone; this difference may allow lead-directed synthesis of other trioxanes to help elucidate the speficity or enhanced drug transport that may mediate drug resistance. Fourth, both trioxanes **6** and **8** were found to be much more potent than Jefford's trioxane **3** in the W-2 Indochina clone.

In summary, alkene oxidative cleavage by $Et_3SiOOOH$ was found sensitive to some very subtle effects of ester and ether oxygen atoms in the substrate alkenes and in oxygen-containing additives. Also, dioxetane formation using $Et_3SiOOOH$ was applied to rapid and easy synthesis of two new and structurally simple trioxanes having substantial and promising antimalarial activity. We are actively pursuing these exciting discoveries for their theoretical as well as their practical value.

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8. A typical experimental procedure for preparation of trioxane **3** is as follows: To the freshly-prepared (<1 minute old) CH_2Cl_2 solution of $Et_3SiOOOH$ (80 mL, 3.2 mmol)[1] at -78°C was cannulated methoxy vinyl ether **1** (63.7 mg, 0.32 mmol) in CH_2Cl_2 (3ml) solution over 10 seconds at under nitrogen atmosphere. To the resultant solution, after being vigorously stirred for 30 min., was slowly added pre-cooled (-78°C) TBDMSOTf (80 μL, 0.35 mmol) in CH_2Cl_2 (1.0 mL) over 1 min. The resultant solution was stirred at -78°C for 15 hours, treated with triethylamine (680 μL, 4.9 mmol), and then slowly warmed to -20°C over one hour and then to room temperature. Column chromatographic purification with ethyl acetate and hexane (2:98) gave 1,2,4-trioxane **3** (42 mg, 58%) as a white solid having the same spectral characteristics as recrystallized material. Recrystallization from hexane afforded white crystals: mp 68-69°C; FT-IR ($CHCl_3$) 3019.7, 2951.5, 2934.1, 2862.1, 1446.0, 1396.8, 1375.5, 1270.4, 1224.2, 1212.4, 1205.8, 1142.6, 1119.9, 1066.3, 1028.8, 1009.0, 972.2, 895.8, 876.7, 865.0, 815.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.93 (s, 1H), 3.52 (s, 3H), 2.30 (ddd, J=14.7, 13.4, 3.8Hz, 1H), 2.05 (ddd, J=14.7, 4.4, 3.1Hz, 1H), 1.86-1.84 (m, 1H), 1.84-1.80(m, 1H) 1.70-1.50 (m, 7H), 1.40 (s, 3H) 1.28-1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 104.93, 104.68, 83.40, 57.08, 47.44, 37.86, 35.69, 30.86, 26.81, 26.22, 25.05, 23.78; CIMS (NH_3) *m/z* (realtive intensity) 246 ($M+NH_4^+$, 100), 229 ($M+H^+$, 42), 214 (39), 211 (71), 197 (63), 196 (59), 186 (20), 179 (60), 169 (92), 151 (36), 138 (89), 125 (33). Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.10; H, 8.83. Found: C, 63.10; H, 8.83.

9. All new compounds were fully characterized by HRMS, IR and 400 MHz ^1H and ^{13}C NMR spectroscopy.

10. Benzyl vinyl ether **7** was prepared by acid catalyzed ether exchange between benzyl alcohol and 3-(2'-methoxy-vinylcyclohexyl)proprionitrile; *cf*, Buchi, G.; White, J.D., *J. Am. Chem. Soc.*, **1964**, *86*, 2884.

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