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Reaction of peroxyacetals with silyl ketene acetals: synthesis of 3-peroxyalkanoates and 3-peroxyalkanals

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Abstract

Lewis acid-mediated reaction of monoperoxyacetals with silyl ketene acetals (SKAs) provides an efficient approach to 3-peroxyalkanoates. Propionate SKAs react with aliphatic peroxyacetals to furnish 3-peroxy-2-methyl alkanoates with modest *anti*-selectivity. Although acetate and thioacetate SKAs are less reactive, the latter react with unsaturated peroxyacetals to furnish peroxyalkenoates and -alkadienoates which undergo chemoselective reduction to 3-peroxyalkenals and 3-peroxyalkadienals. © 2000 Elsevier Science Ltd. All rights reserved.

Peroxyalkanoates are common substructures in cyclic peroxide natural products, as well as potentially useful synthetic intermediates.[1] However, methodology for synthesis of this motif remains limited.[2,3] In contrast, 3-alkoxyalkanoates are readily available via reaction of silyl ketene acetals (SKAs) and acetals.[4] We recently reported a new approach to peroxide synthesis based upon Lewis acid-mediated reactions of peroxyacetals with allylsilanes and silyl enol ethers.[5,6] We now report the synthesis of 3-peroxyalkanoates through corresponding reactions of peroxyacetals with SKAs (Fig. 1). In addition, we demonstrate the chemoselective conversion of peroxyalkanoates to peroxyalkanals.

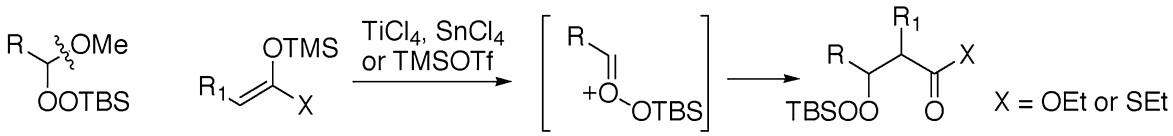

Figure 1. Lewis acid-mediated addition to peroxyacetals

Aliphatic (**1a**,**1b**) and benzylic (**2a**,**2b**) peroxyacetals were prepared through ozonolysis of alkenes or enol ethers in methanol or 2-methoxyethanol, followed by silylation of the resulting

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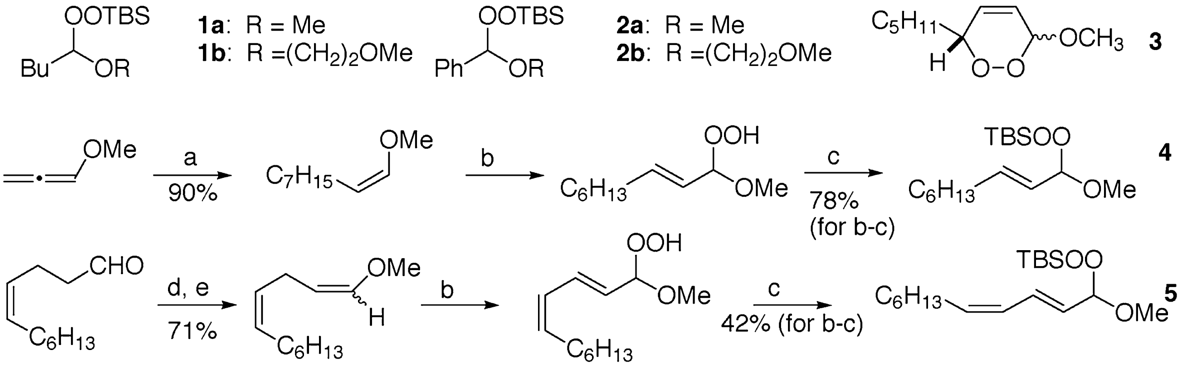
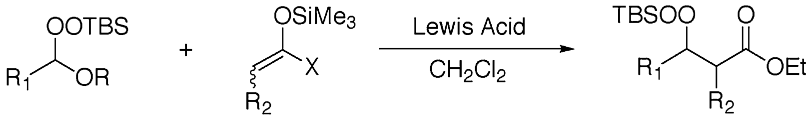
hydroperoxyacetals (Scheme 1).[7–10] Peroxyacetal **3** was obtained from 13-hydroperoxyoctadecadienoic acid using a reported procedure.[11] Synthesis of allyl peroxyacetal **4** was achieved through *tetra*-perfluoropropylporphyrin (TPFPP)-sensitized photooxygenation[12,13] of an enol ether,[14] followed by silylation of the hydroperoxyacetal.[9] The diene peroxyacetal **5**, prepared similarly from a dienol ether,[15] decomposed exothermically upon chromatography and was used without purification.



Scheme 1. Peroxyacetal substrates: (a) hexylMgBr, CuBr; (b) TPFPP, O_2, hν, CCl_4; (c) TBSCl, Imid.; (d) $HC(OMe)_3$, TsOH; (e) TMSOTf, *i*-Pr_2NEt

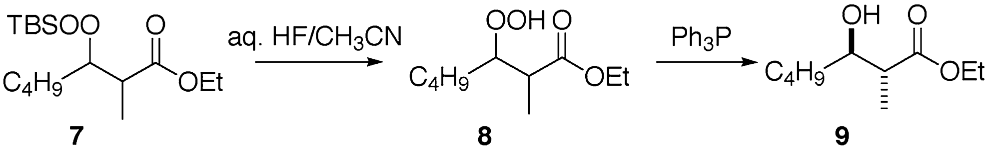
Reactions of aliphatic peroxyacetal **1a** with the SKAs of ethyl acetate or ethyl thioacetate failed to produce the peroxyalkanoate. The corresponding reaction with the SKA of benzyl acetate, although occasionally successful, was not consistently reproducible. In contrast, reaction with (*E*)- or (*Z*)-propionate SKAs[16] reproducibly furnished 3-peroxy-2-methyl alkanoates **7** as a mixture of easily distinguished (^{1}H) diastereomers. Reaction of the propionate SKAs with the benzylic peroxyacetals **2a** and **2b** proceeded in higher yield but without diastereoselection (Table 1).

Table 1
Synthesis of 3-peroxy-2-methylalkanoates



subs.	R	R_1	R_2	X	geometry	Lewis acid	T (°C)	t (h)	Prod.	Yield(%)	syn/anti
1a	Me	Bu	H	OEt	-	$SnCl_4$ (1.0)	-30	1	-	-	na
1a	Me	Bu	H	OEt	-	TMSOTf (0.1)	-30	1	-	-	na
1a	Me	Bu	H	OBn	-	TMSOTf (1.0)	-30	1	**6**	0-50%	na
1a	Me	Bu	H	SEt	-	TMSOTf (0.1)	-30	1	-	-	na
1a	Me	Bu	Me	OEt	E	$SnCl_4$ (1.0)	0	6	**7**	-	-
1a	Me	Bu	Me	OEt	E	TMSOTf (0.1)	0	6	**7**	85	30:70
1a	Me	Bu	Me	OEt	Z	TMSOTf (0.1)	0	6	**7**	35	33:66
1b	$(CH_2)_2OMe$	Bu	Me	OEt	E	$TiCl_4$ (1.0)	-78 - 0	4	**7**	79	29:71
1b	$(CH_2)_2OMe$	Bu	Me	OEt	E	TMSOTf (0.1)	0	24	**7**	52	30:70
2a	Me	Ph	Me	OEt	E	TMSOTf (0.1)	0	6	**8**	90	1:1
2b	$(CH_2)_2OMe$	Ph	Me	OEt	E	$TiCl_4$ (1.0)	-78 - 0	6	**8**	92	1:1

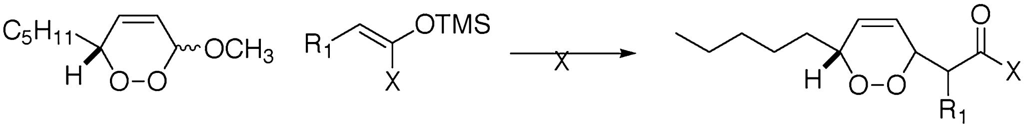
The relative stereochemical configuration of the 3-peroxy-2-methylheptanoates **7** was assigned following deprotection and reduction to furnish a 70:30 mixture of *anti* and *syn*-3-hydroxy-2-methylalkanoates **9** (Fig. 2).[17] Interestingly, deprotection with *n*-Bu_4NF resulted in isolation of **8** and **9** as a 50:50 mixture of *syn*- and *anti*-diastereomers. The ability to achieve epimerization without decomposition, a potentially useful approach to *syn*-peroxypropionates, is surprising given the intermediacy of 3-peroxyenolates in nucleophilic epoxidations.[18]



(major shown)

Figure 2. Stereochemical correlation

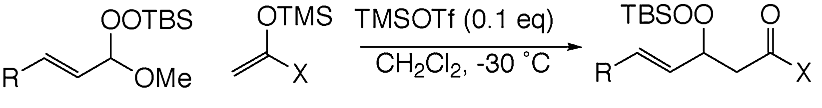
Alkoxydioxine **3** failed to react with acetate, thioacetate, or propionate SKAs, instead undergoing slow decomposition. The formation of allylated dioxane[11] upon addition of allytrimethylsilane verified the presence of a reactive intermediate, suggesting the lack of reaction with the more nucleophilic SKAs[19] may simply be due to decomposition under the prolonged reaction conditions (Fig. 3).



R_1	X
H	OEt
Me	OEt
H	SEt

Figure 3. Attempted synthesis of dioxine acetates and propionates

Allyl acetal **4** reacted with the SKAs of benzyl acetate, *t*-butylthioacetate, and ethyl thioacetate to furnish 3-peroxyalkenoates. The labile diene peroxyacetal **5** reacted with the trimethylsilyl SKA of ethyl thioacetate to produce the peroxyalkadienoate thioester (Fig. 4). The peroxyalkenoates and -alkadienoates were stable, easily purified, compounds.



R	X	Yield
hexyl	OBn	68
hexyl	S-*t*-Bu	41
hexyl	SEt	47
(*Z*)-1-octenyl	SEt	42

Figure 4. Synthesis of peroxyalkenoates

Chemoselective reduction of the 3-peroxyalkenoate and 3-peroxyalkadienoate thioesters was investigated as a possible approach to synthetic precursors of hydroperoxyeicosatetraenoic acids (HPETEs). For both the allyl and dienyl series, low temperature DIBAL reduction proceeded in moderate to good yield to produce stable 3-peroxyaldehydes (Fig. 5).

R	Yield
hexyl	78%
1-(*Z*)-octenyl	50%

Figure 5. Synthesis of peroxyalkenals

In conclusion, reaction of silyl ketene acetals with peroxyacetals provides an efficient approach to 3-peroxyalkanoates and 3-peroxyalkanals. Investigation of asymmetric versions of this transformation and applications to the total synthesis of peroxide natural products are in progress.

Acknowledgements

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10. Except where noted, all new compounds were purified and characterized by standard procedures. Typical reaction conditions: To a solution of peroxyacetal (1.0 mmol) and silyl ketene acetal (1.25 mmol) in CH_2Cl_2 (10 mL) at –20°C is added TMSOTf (0.1 mmol). The completed reaction (TLC) is quenched by rapid addition of EtOAc (10 mL) and $NaHCO_3$ (10 mL). The separated organic layer is washed with water (10 mL) and dried with Na_2SO_4, with the concentrated residue subjected to flash chromatography (EtOAc/hexanes) on silica gel containing 1% v/v of Et_3N. Ethyl-2-methyl-3-[(1,1-dimethylethyl)dimethylsilyl)dioxy]heptanoate: *anti* (determined from mixture): $R_f = 0.53$ in 10% EA/hexane; ^{1}H NMR 4.23 (m, 1H), 4.10 (m, 2H), 3.08 (qd, 1H, $J = 7.16$, 5.60), 1.08 (d, 3H, $J = 7.16$), 1.40–0.80 (18H), 0.8 (s, 6H). Anal. calcd for $C_{15}H_{34}O_4Si$: C, 60.33; H, 10.76. Found: C, 60.24; H, 10.74. Ethylthio (4*E*)-3-(1,1-dimethylethyldimethylsilyldioxy)-4-undecenoate: $R_f = 0.6$ (10% EtOAc/hexanes); ^{1}H NMR (300 MHz) 5.73 (dt, 1H, $J = 15.2$, 6.7), 5.35 (ddt, 1H, $J = 15.5$, 7.8, 1.4), 4.71 (q, 1H, $J = 6.7$), 3.08 (dd, 1H, $J = 14.5$, 6.2), 2.84 (q, 2H, $J = 7.4$), 2.66 (dd, 1H, $J = 14.8$, 6.7), 2.01 (q, 2H, $J = 6.7$), 1.39–1.19 (m, 11H), 0.93–0.83 (m, 12H), 0.13 (s, 6H); ^{13}C NMR (75 MHz) 196.4, 137.0, 126.2, 82.6, 47.6, 32.3, 31.7, 28.8, 28.7, 26.1, 25.6, 23.3, 22.6, 18.1, 14.1, –5.7; IR (neat): 1698 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{38}O_3SSi$ $(M+Li)^+$: 381.2327. Found: 381.2471.
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