Communications

Peroxycarbenium-Mediated C–C Bond Formation: Synthesis of Cyclic Peroxides from Monoperoxyketals

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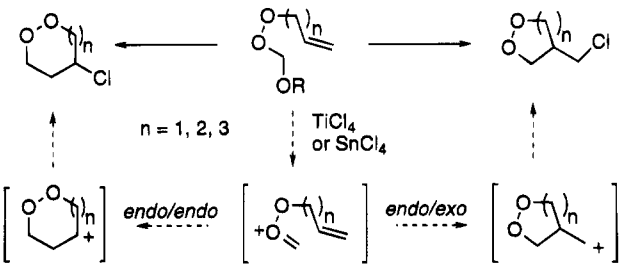
Although the growing inventory of cyclic peroxide natural products[1] has attracted increasing synthetic attention, the instability of the peroxide group has constrained most approaches to strategies accommodating final-step introduction of one or both peroxide C–O bonds; typical examples include cyclization of unsaturated hydroperoxides and addition of $^1O_2$ to dienes.[2,3] Our laboratory has been investigating new methodology based upon carbon–carbon bond formation in the presence of the peroxide linkage, and we recently discovered a new approach to dialkyl peroxides based upon intermolecular displacement of monoperoxyketals by allyltrimethylsilane and other electron-rich alkenes in the presence of Lewis acids.[4] We realized that the corresponding *intramolecular* reaction would not only constitute a powerful new approach to the synthesis of cyclic peroxides but might, due to entropic advantages, be applicable to simple alkene nucleophiles. We now report a successful new approach to 1,2-dioxanes, 1,2-dioxepanes, and 1,2-dioxocanes based upon the cyclization of peroxycarbenium ions derived from unsaturated monoperoxyketals (Scheme 1).

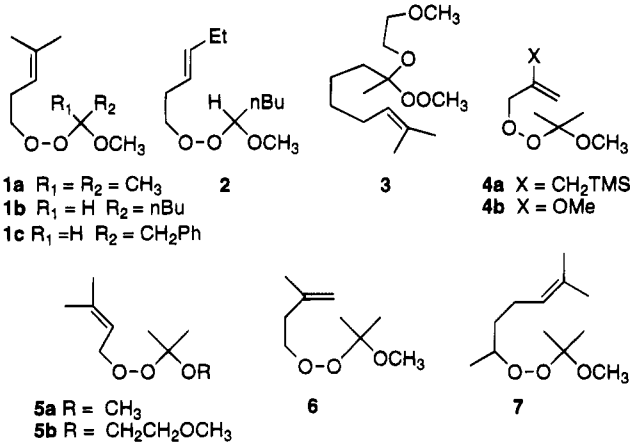
The substrates for cyclization studies are shown in Scheme 2. Monoperoxyketals **1a**, **4ab**, **5a**, **6**, and **7** were prepared through alkylation of 2-methoxyprop-2-yl hydroperoxide with the appropriate alkyl bromide, iodide, or sulfonate.[5,6] Monoperoxyacetals **1b** and **2** were obtained through the analogous alkylation of 1-methoxypent-1-yl hydroperoxide while **1c** was obtained upon acid-catalyzed addition of 4-methyl-3-pentenyl hydroperoxide to 2-methoxystyrene. Monoperoxyketal **3** was obtained from 6-hydroperoxy-6-(2-methoxyethoxy)-6-hexanal[7] through sequential alkylation and Wittig olefination.[8] Monoperoxyketal **5b** was obtained upon alkylation of 1-(2-methoxyethoxy)-1-methylethyl hydroperoxide, available through ozonolysis of dimethylbutene in 2-methoxyethanol.[9]

Intramolecular attack of alkenes onto peroxycarbenium ions, much like reactions of corresponding oxycarbenium ions, can be classified by the *exo* or *endo* relationship of both the electrophilic peroxycarbenium ion and the

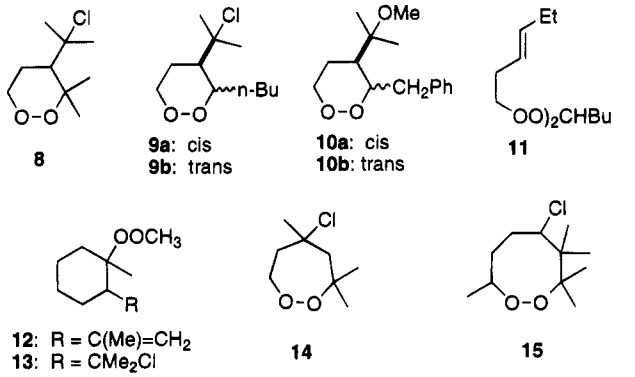
Scheme 1



Scheme 2



Scheme 3



nucleophilic alkene to the newly forming ring (Scheme 1).[10] Addition of either $TiCl_4$ or $SnCl_4$ to a chilled solution of perketal **1a** afforded 1,2-dioxane **8** in good yield through a 6-*endo*/*exo* pathway[11] (Scheme 3 and Table 1). In pleasant contrast to the corresponding intermolecular reactions, cyclization was also successful for less stabilized peroxycarbenium ions; monoperoxyacetal **1b** underwent cyclization to a 2.6:1 *cis*/*trans* mixture of dioxanes **9a**:**9b** while **1c** reacted to furnish a 6:1 *cis*/*trans* mixture of dioxanes **10a**:**10b** in which the displaced

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(6) Yields for preparation of starting materials: **1a** (75%); **1b** (62%); **1c** (45%); **2** (26%); **3** (3 steps, 5% overall); **4a** (13%); **4b** (7%); **5a** (51%); **5b** (48%); **6** (39%); **7** (42%).
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(11) Typical procedure: To a −78 °C solution of monoperoxyacetal (1 mmol) in CH_2Cl_2 (3 mL) under an atmosphere of N_2 was added 0.95 mL of a nominally 1.0 M solution of $TiCl_4$ in CH_2Cl_2. The resulting solution was stirred at −78 °C for 30 min and then quenched with water. The ether extract was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was directly subjected to flash chromatography on silica gel. All new compounds have been fully characterized by ^1H NMR, ^{13}C NMR, IR, and satisfactory elemental analysis (±0.4%).

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Table 1

entry	substrate	conditions (all reactions at −78 °C)		products	yield (%)
1	**1a**	$TiCl_4$	30 min	**8**	64
2	**1a**	$SnCl_4$	30 min	**8**	73
3	**1b**	$SnCl_4$	4 h	**9ab**	68 (2.6:1)
4	**1c**	$TiCl_4$	20 min	**10ab**	20 (5.7:1)
5	**2**	$SnCl_4$	2 h	**11**	
6	**3**	$TiCl_4$	5 min	**12**	18 (1.9:1)
				13	26 (7.2:1)
7	**4a**	$TiCl_4$	2 h		
8	**4b**	$TiCl_4$	2 h		
9	**5a**	$TiCl_4$	1 h		
10	**5b**	$TiCl_4$	10 min		
11	**6**	$TiCl_4$	2 h	**14**	46
12	**7**	$TiCl_4$	8 min	**15**	16 (2.4:1)

methoxyl leaving group also acts as a cation trapping agent.[12] However, even the intramolecular cyclizations remain ultimately limited by alkene nucleophilicity; disubstituted alkene **2** underwent acid-catalyzed disproportionation to diperoxyacetal **11** in lieu of cyclization.[13]

The cyclizations of unsaturated monoperoxycarbenium ions appear to have stereoelectronic constraints not previously observed in related systems. Cyclization of monoperoxyketal **3** through a 6-*exo/exo* mode was successful, affording dioxolanes **12** and **13**, each as an *cis/trans* mixture. However, no dioxanes were isolated from attempted cyclization of **4a** or **4b**, even though 6-*endo/endo* cyclizations of oxycarbenium ions are well-precedented.[14-19] Similarly, although 5-*endo-trig* closures have been observed in cyclizations of acetal-derived oxycarbenium ions,[14,18,20] all attempts to synthesize 1,2-dioxolanes through the corresponding 5-*exo/endo* cyclizations of **5a** or **5b** were also unsuccessful.

Peroxycarbenium ion cyclizations do offer an entry to medium-ring peroxides. Reaction of monoperoxyacetal **6** with $TiCl_4$ afforded the expected dioxepane **14** derived from 7-*endo/endo* cyclization in 46% yield. However, monoperoxyacetal **7** failed to undergo cyclization through the expected 7-*exo/endo* mode; closure instead occurred in an 8-*endo/endo* mode to furnish a 16% yield of 1,2-dioxocane **15** as a 2.4:1 ratio of diastereomers. A similar outcome has been observed during corresponding cyclizations of unsaturated oxycarbenium ions.[21,22]

In summary, we have demonstrated that the chemoselective activation of monoperoxyacetals or -ketals with $SnCl_4$ or $TiCl_4$ produces an intermediate, presumably a peroxycarbenium ion, capable of undergoing intramolecular reaction with simple alkenes to furnish 1,2-dioxanes, 1,2-dioxepanes, and 1,2-dioxacanes. The success of cyclizations thorough 6-*endo/exo*, 6-*exo/exo*, 7-*endo/endo*, or 8-*endo/endo* pathways, combined with the failure to observe products derived from 5-*endo/exo*, 6-*endo/endo*, or 7-*endo/exo* cyclizations, implies the possible existence of stereoelectronic constraints unique to peroxycarbenium ions. Further investigations into the scope and mechanism of this new reaction will be reported in due course.

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Supplementary Material Available: ^1H NMR spectra of **1**−**15** and unnumbered synthetic precursors (29 pages).

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(12) Due to overlapping signals in the NMR spectrum the *cis* and trans isomers of **9** were assigned by analogy to **10ab**, whose ^3J_H across the newly formed bond were as follows: **10a** (cis) = 3.3 Hz; **10b** (trans) = 9.7 Hz. In addition, **10a** displayed 2−4% NOE enhancements between H_5 (axial) and the benzylic hydrogens.

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