Peroxycarbenium-Mediated C–C Bond Formation: Synthesis of Peroxides from Monoperoxy Ketals

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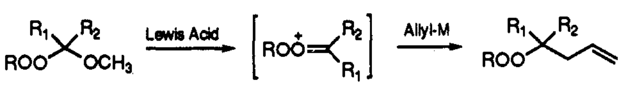
Despite the importance of peroxides in biology, chemistry, and medicine, synthetic approaches toward peroxide-containing natural products are seriously constrained by the limited number of methods available for incorporation of the peroxide group. At present, peroxide introduction is nearly always accomplished via nucleophilic displacement or direct dioxygenation.[1] Research in our labs has introduced new synthetic strategies for peroxide synthesis based upon chemoselective formation of carbon-carbon bonds in the presence of protected peroxides.[2] Recently, we became interested in the development of reactions in which the peroxide group would not merely survive a bond-forming process but would actually mediate formation of neighboring bonds. We now report a new method for peroxide synthesis based upon the addition of nucleophilic alkenes to peroxycarbenium ions derived from monoperoxy ketals (Scheme I).

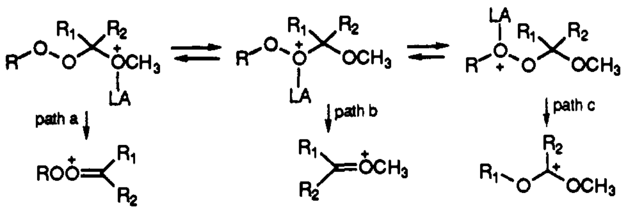
The Lewis-acid-mediated reaction of ketals and acetals with electron-rich alkenes, proceeding via intermediate oxocarbenium ions, is a powerful method for the construction of homoallyl ethers and 3-alkoxycarbonyl units.[3] As the analogous monoperoxy ketals and monoperoxy acetals are readily available from a variety of precursors, the Lewis-acid-mediated reaction between peroxycarbenium ions and electron-rich alkenes would provide an extremely versatile methodology for peroxide synthesis.[4a–d] However, one possible complication is the requirement for chemoselective activation of the monoperoxy ketal. Interaction with a Lewis acid (LA) could be imagined to occur through any one of three manifolds (Scheme II). Formation of a Lewis acid–alkoxide complex (path a) will allow for selective alkoxide displacement, either directly or through a peroxycarbenium ion. Alternatively, complexation of the anomeric peroxide oxygen could lead to undesired loss of the peroxide group (path b). Finally, complexation of the remote peroxide oxygen (path c) would be expected to initiate heterolytic fragmentation.[4e]

Several monoperoxy ketals were prepared to test this proposed methodology[5] (Scheme III). Alkylation of 2-methoxypropyl hydroperoxide with octyl bromide directly furnished **1a**.[6] Monoperoxy ketal **1b** was obtained upon addition of octyl hydroperoxide to methoxycyclohexene. Alkoxy endoperoxide **1c** was produced upon photocyclization of 4(*S*)-hydroperoxy-2(*E*)-nonenal, available upon deprotection of an enantiomerically pure peroxyaldehyde.[2b,7] Initial reaction conditions were chosen so as to minimize contact time between the monoperoxy ketals and the Lewis acid. Addition of $TiCl_4$ to a –78 °C solution of **1a** and allyltrimethylsilane in CH_2Cl_2 led to the rapid disappearance of starting material and the isolation of homoallyl peroxide in modest yield. Repetition of this procedure with **1b** furnished very little peroxide. In contrast, addition of allyltrimethylsilane to a –78 °C solution containing $TiCl_4$ and either **1a** or **1b** provided good to excellent yields of peroxides **2a** or **2b**. The dramatic improvement brought about by this alternate order of addition illustrates the surprising stability of the monoperoxy ketals toward Lewis acids, and a version of this procedure was subsequently employed for all substitutions.[8] Substitutions with allyltributylstannane also led to excellent yields of homoallyl peroxides from either **1a** or **1b**; similarly, $TiCl_4$-mediated reaction of monoperoxy ketal **1a** with an enol ether efficiently provided peroxy ketone **3a**. Although $SnCl_4$ was also found to effectively mediate allylations, other Lewis acids (BF_3, TMSOTf, or $EtAlCl_2$) were clearly inferior.

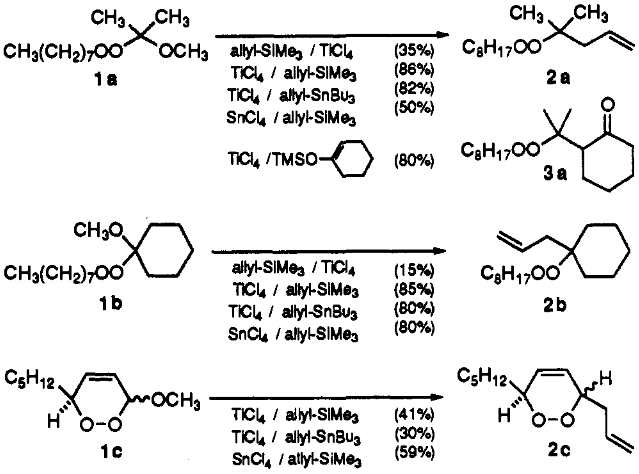
Scheme I



Scheme II



Scheme III



Displacement of a secondary allylic monoperoxy acetal (**1c**) also proceeded rapidly in the presence of either $TiCl_4$ or $SnCl_4$ to produce moderate yields of the 3-allyl endoperoxide as a 3:2 mixture of the cis/trans diastereomers.[9] However, attempted allylation of the corresponding saturated monoperoxy acetal, available upon hydrogenation of **1c** over PtO_2, was unsuccessful.

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[6] Compounds **1a–c**, **2a–c**, and **3a** have been fully characterized by ^1H NMR, ^{13}C NMR, IR, and satisfactory elemental analyses (±0.4% for C and H).

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[8] Typical procedure: To a –78 °C solution of monoperoxy ketal **1a** (87 mg, 0.4 mmol) in CH_2Cl_2 (3 mL) under an atmosphere of N_2 was added $TiCl_4$ (0.4 mmol) as a 1 M solution in CH_2Cl_2. After 3 min, a solution of allyltrimethylsilane (59 mg, 1.3 equiv) in CH_2Cl_2 (1 mL) was added, and the reaction was stirred for 1 h. The reaction was quenched with water, and the products were extracted with hexane. After drying of the mixture and removal of solvent *in vacuo*, flash chromatography (5% ethyl acetate/hexane) afforded 79 mg (86%) of the pure homoallyl peroxide **2a** as a colorless oil.

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In summary, we have demonstrated a new method for the synthesis of peroxides through peroxide-mediated carbon–carbon bond formation. Despite initial fears regarding the compatibility of the peroxide moiety toward Lewis acids, it is clear that the reactive intermediate, either a complexed monoperoxy ketal or a peroxycarbenium ion, enjoys surprising stability at low temperature. Investigations into the scope and limitations of this new methodology for the formation of both peroxides and hydroperoxides are in progress.

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