Oxacycle Synthesis via Intramolecular Reaction of Carbanions and Peroxides

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3 Supporting Information

ABSTRACT: The intramolecular reaction of dialkyl peroxides with carbanions, generated via chemoselective metal-heteroatom exchange or deprotonation, provides a new approach to cyclic ethers. Applied in tandem with C−C bond formation, the strategy enables a one-step annelation to form oxaoospirocycles.

Ethers, which comprise critical substructures in many bioactive molecules and natural products,1 are typically synthesized through attack of nucleophilic oxygen on an electrophilic carbon.1,2 The converse of this strategy, attack of a carbanion on electrophilic oxygen, has been investigated to only a limited extent for intermolecular reactions and is essentially unexplored for intramolecular reactions. We now demonstrate that chemoselective generation of carbanions in the presence of appropriately positioned O−O bonds of dialkyl peroxides allows the efficient introduction of cyclic ethers (Figure 1), including frameworks (for example, 15a or 19b, vide infra) challenging to approach via existing methodology.

Previous reports have described the intermolecular reaction of simple organometallics with dialkyl peroxides,3 peresters,4 and endoperoxides.5 Bissilyl peroxides and lithiated hydroperoxides have been applied to oxygenation of lithiated arenes and alkenes.6,7 However, the only precedent for the corresponding intramolecular reactions of carbanions with peroxides is the 3-exo cyclization of short-lived enolate intermediates formed during nucleophilic epoxidation reactions.8

At the outset of these studies, we faced two major uncertainties: first, would it be possible to generate reactive carbanions in the presence of a peroxide; and, second, would the carbanion/peroxide pair undergo intramolecular C−O bond formation. The question of chemoselective generation of an organolithium nucleophile was initially investigated using a dialkyl peroxide (1) derived from reaction of t-butyl hydroperoxide with dihydrogeraniol methanesulfonate.9 Consistent with previous observations,5a reaction of 1 with n-BuLi proceeded readily to furnish butyl ether 2 (eq 1). Repeating this reaction in the presence of a slight excess of allyltributylstannane resulted in predominant formation of the allyl ether (3), demonstrating that Li/heteroatom exchange proceeds much more rapidly than C−O bond formation.

Confident of our ability to selectively generate a carbanion in the presence of a peroxide, we prepared a family of substrates (6a−c and 9) incorporating a dialkyl peroxide and a precursor aryllithium precursor (Scheme 1). The peroxide was either installed via displacement of a sulfonate (base) or iodide (Ag2O).10 The lower yield for phenethyl peroxide 9 reflects a tendency for Kornblum elimination in this skeleton.11

Scheme 1. Synthesis of Aryl Peroxide Substrates

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Table 1 illustrates the results of metal-heteroatom exchange for peroxides 6a–c and 9. Addition of either n-BuLi or PhLi to

\[ \text{peroxide} + \text{Li} \rightarrow \text{dihydrobenzopyran} \]

a–78 °C solution of 6a (iodide) or 6b (bromide), followed by warming of the reaction mixture to 0 °C, afforded good yields of dihydrobenzopyran 10. The corresponding reactions of the tributylstannyl arene (6c) proceeded in much lower yield (PhLi) or essentially not at all (BuLi). Lithiation of o-iodophenethyl peroxide 9 furnished dihydrobenzofuran in excellent yield.

Repeating the lithiation of 6a and quenching the reaction with MeOH-d₄ prior to warming resulted in formation of a monodeuterated peroxide (eq 2), demonstrating that lithiation occurs more rapidly and at lower temperature than intramolecular C−O bond formation.

\[ \text{6a} + \text{MeOH-d}_{4} \rightarrow \text{product} + \text{d}_{4} \]

We next investigated corresponding cyclizations of enolate anions, prepared as illustrated in Scheme 2.

Conditions for cyclization were initially investigated for the 5-exo closure of peroxide 14b (Table 2). The reaction, which generates tert-butoxide anion as a byproduct, proceeded rapidly in THF in the presence of KOtBu or KH. Only traces of products were observed using LDA.

Scheme 2. Synthesis of Peroxyketones

Table 2. Investigation of Cyclization Conditions

| base      | equiv | isolated yield |
|-----------|-------|----------------|
| KOt-Bu    | 0.5   | 81% (99)       |
| KOt-Bu    | 1.0   | 85%            |
| KOt-Bu    | 2.0   | 88% (99)       |
| KH        | 1.0   | 86% (99)       |
| KH        | 2.0   | 89%            |
| LDA       | 1.0   | NR             |

*GC yields. †Isolated yield.

The transformation was not limited to aryl ketones, as evidenced by cyclization of peroxyhexanone 16 (eq 3); the volatile product was isolated after homologation with a Horner–Emmons reagent.

Finally, we investigated the reaction of enolates with a series of t-butyl iodoalkyl peroxides 18a–d, available in one step from the corresponding 1,ₙ-dihalides (Table 4). The results demonstrate the ability to achieve, in one step, a high-yielding annelation of spiropylic ethers onto ketone frameworks, opening the door to a class of spiropylics previously approachable mainly through cationic ring expansions. The isolation of the homologated peroxide 20 during attempted formation of a 7-membered ring provides strong evidence that the formation of the 5- and 6-membered spiropylic proceeds via initial formation of a C–C bond.
In conclusion, we have demonstrated the chemoselective generation of carbanions in the presence of dialkyl peroxides and the application of the resulting intermediates to establish new C−O bonds. This alternative to more traditional ethersifications provides a new approach to synthesis of spirocyclic ethers, aryl ethers, and various oxacycles including oxetanes.

ASSOCIATED CONTENT

Supporting Information
Experimental procedures, spectral listings, and selected 1H and 13C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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