Radical Deoxygenation of Hydroxyl Groups via Phosphites
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Deoxygenation of alcohol hydroxyl groups continues to play an indispensable role in the synthesis of organic compounds, particularly complex natural products containing multifunctional groups. Among plenteous methods at our disposal for effecting such transformations, the radical reaction of a large array of O-thiocarbonyl derivatives, the Barton–McCombie reaction, is possibly the most versatile and widely employed by practicing synthetic chemists, owing to its phenomenal functional group tolerance. The method has been exceptionally effectual for the deoxygenation of secondary alcohols, whereas its application to the deoxygenation of primary and tertiary alcohols has met with mixed results. In addition, the formation of side products often has been recognized. Therefore, the development of an alternate method for the deoxygenation of alcohols that obviates these drawbacks would be highly desirable.

Phosphoranyl radicals, $\text{X} = \text{P}$, are most commonly generated by radical addition to trivalent phosphorus molecules and have appreciable lifetimes. Depending upon the nature of the ligands on phosphorus, these phosphoranyl radicals can adopt either trigonal bipyramidal or quasi-tetrahedral structures with the single electron confined to a $\pi$ antibonding orbital or delocalized to $\pi$-acceptor ligands. Phosphoranyl radicals of type $\text{R} = \text{P} - \text{X}$ may undergo either $\alpha$-scission with the cleavage of a $\text{P} - \text{R}^\prime$ bond or $\beta$-scission with the cleavage of the $\text{X} - \text{R}$ bond (Scheme 1). While $\alpha$-scissions correspond to overall homolytic substitutions at the phosphorus, $\beta$-scissions result in the oxidation of phosphorus(III) to phosphorus(V) and, importantly, the deoxygenation of $\text{R} - \text{OH}$ when $\text{X} = \text{O}$. In the following, we describe an efficient method for the radical-based deoxygenation of an alcohol group by the use of its phosphite derivative.

We envisaged that the deoxygenation of alcohols could be achieved by a two-step sequence (Scheme 2); alcohol 2 is first converted into its trivalent phosphorus derivative 3, and then the aryl radical generated under standard radical conditions could intramolecularly attack the phosphorus atom to form the phosphoranyl radical 4. It was expected that the presence of a benzene ligand would impede the $\alpha$-sission pathway. Consequently, the fragmentation of radical 4 by the $\beta$-scission would likely be favored, producing the radical (R') which should lead to the reduction product R-H upon hydrogen abstraction.

Our initial attempt employing the [2-(2′-iodophenyl)phenyl]-phenylphosphinite derivative of an alcohol resulted in the formation of a complex mixture. However, the use of a phosphite derivative 3 [R = OMe; X = O; n = 2] resulted in clean formation of the reduction product, $\text{R} = \text{OH}$, thus overall constituting highly efficient deoxygenation of alcohols.

The preparation of the phosphite derivative was readily achieved by successive treatments of an alcohol with $\text{CH}_3\text{OPCl}_3$ and 2-(2′-iodophenyl)ethyl alcohol (Scheme 3). Upon subjection of phosphite 9 to standard radical conditions [(n-Bu)$_3$SnH (1.4 mol equiv), AIBN (cat), benzene, reflux, 2 h], the phosphite 9 was all consumed, and the corresponding deoxygenation product 13 and phosphonate 11 were isolated each in 62% yield. In addition, phosphonate 14 was also obtained in 29% yield. The formation of 13 (as well as 11) and phosphonate 14 is the result of the $\beta$-scissions of the PO-R (route a) and the RO-CH$_3$ groups (route b), respectively. In view of the synthetic potential of the reaction to

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Scheme 1. Fragmentation of Phosphoranyl Radicals

Scheme 2. Phosphorus-Mediated Deoxygenation Pathway

Scheme 3. Radical Deoxygenation through a Phosphate Intermediate and Competition between the Two $\beta$-Scission Processes

*Reagents and conditions: (i) $\text{Cl}_3\text{POCH}_3$ (2.5 mol equiv)/[(n-Pr)$_3$NEt (7.5 mol equiv)/THF, $-78^\circ$C; 2-(2′-iodophenyl)ethanol (3.5 mol equiv), $-78^\circ$C to room temperature. (ii) (n-Bu)$_3$SnH (1.4 mol equiv), AIBN (cat)/benzene, reflux, 2 h.

equiv), AIBN (cat), benzene, reflux, 2 h], phosphite 9 was all consumed, and the corresponding deoxygenation product 13 and phosphonate 11 were isolated each in 62% yield. In addition, phosphonate 14 was also obtained in 29% yield. The formation of 13 (as well as 11) and phosphonate 14 is the result of the $\beta$-scissions of the PO-R (route a) and the RO-CH$_3$ groups (route b), respectively. In view of the synthetic potential of the reaction to
Table 1. Preparation of Phosphites 15 and Radial Deoxygenation of Alcohols 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Phosphite 15 yield (%)</th>
<th>R-H (7); yield from 15 (%)</th>
<th>11:16</th>
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<tr>
<td>1</td>
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<td>80&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>85&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>88&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
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<td>&gt;98&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>7</td>
<td>JCH</td>
<td>85</td>
<td>87&lt;sup&gt;g&lt;/sup&gt;&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1:0</td>
</tr>
</tbody>
</table>

<sup>a</sup> See conditions i and ii, respectively, in Scheme 3.  
<sup>b</sup> Yield of isolated, chromatographically pure products.  
<sup>c</sup> The ratio of the products from the PO-R bond scission and the scission of PO-CH<sub>3</sub> bonds. Estimated by integrations of the corresponding peaks in the <sup>1</sup>H and <sup>3</sup>1 P NMR spectra of the crude reaction mixture.  
<sup>d</sup> Yield estimated by GC-MS using n-decane as an internal standard.  
<sup>e</sup> 17<sup>β</sup>-Methyl product.

group seems to indicate that the intermediate phosphoryl radical adopts most likely not a trigonal bipyramidal structure, but other structures such as a quasi-tetradeiral ligand π-electronic structure where the single electron is delocalized throughout the benzene ring.  

If a trigonal bipyramidal radical structure were close to that of the transition state for the β-scission, one would expect bulky groups to be preferentially attached to the resulting phosphonate product instead of being involved in the fragmentation pathway, as observed by Barton  

in the preparation of highly hindered phosphates from phosphites. Regardless of the transition-state structure in the system examined here, there seems to be site selectivity for β-scission involving the bulkier or more substituted carbon center occupying that site.

In summary, we have developed a highly versatile method for the deoxygenation of alcohols. This two-step sequence is highly efficient, particularly for the deoxygenation of relatively hindered alcohols, including tertiary alcohols. The purification of the deoxygenation product is readily achieved, as the phosphonate byproducts are considerably more polar.

Supporting Information Available: Spectral data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

References


JA0462777