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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,[1] 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,[2] 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[3,4] and tertiary alcohols[5] 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.

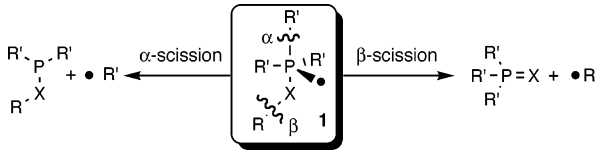
Phosphoranyl radicals, $X_4P^{\bullet}$, are most commonly generated by radical addition to trivalent phosphorus molecules and have appreciable lifetimes.[6] Depending upon the nature of the ligands on phosphorus, these phosphoranyl radicals can adopt either trigonal bipyramidal or quasi-tetrahedral structures with the single electron confined to a P−X antibonding orbital or delocalized to π-acceptor ligands.[6] Phosphoranyl radicals of type $R'_3P^{\cdot}-XR$ may undergo either α-scission with the cleavage of a P−R′ bond or β-scission with the cleavage of the X−R bond (Scheme 1). While α-scissions correspond to overall homolytic substitutions at the phosphorus,[7] β-scissions result in the oxidation of phosphorus(III) to phosphorus(V) and, importantly, the deoxygenation of R−OH when X = O.[8] 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 α-sission pathway.[9] Consequently, the fragmentation of radical **4** by the β-scission would likely be favored, producing the radical ($R^{\bullet}$) which should lead to the reduction product R−H upon hydrogen abstraction.

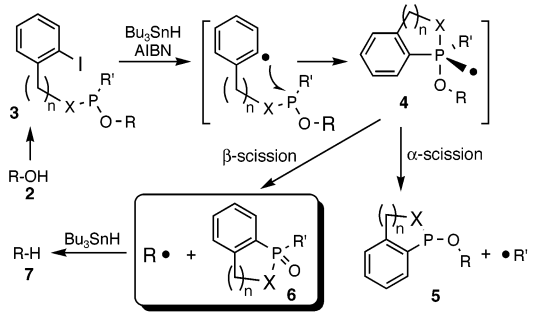
Our initial attempt emplyoing the [2-(2′-iodophenyl)phenyl]-phenylphosphinite derivative of an alcohol resulted in the formation of a complex mixture.[10] However, the use of a phosphite derivative **3** [R′ = OMe; X = O; n = 2] resulted in clean formation of the reduction product, **7**,[6] thus overall constituting highly efficient deoxygenation of alcohols **2**.

The preparation of the phosphite derivative was readily achieved by successive treatments of an alcohol with CH_3OPCl_2 and 2-(2′-iodophenyl)ethyl alcohol[11] (see **8** → **9**, 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], 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 β-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

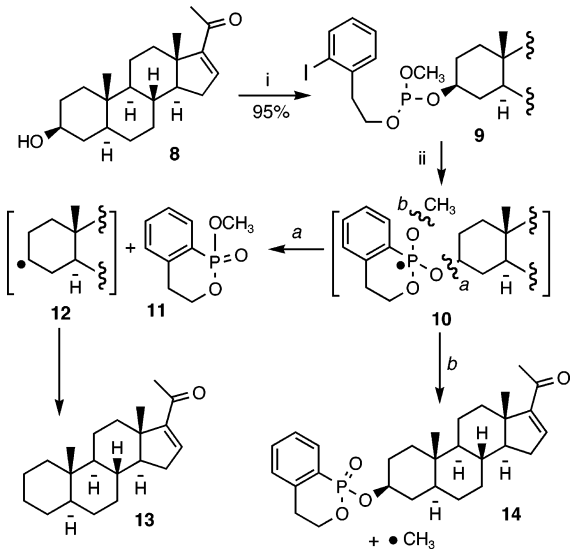
Scheme 1. Fragmentation of Phosphoranyl Radicals



Scheme 2. Phosphorus-Mediated Deoxygenation Pathway



Scheme 3. Radical Deoxygenation through a Phosphite Intermediate and Competition between the Two β-Scission Processes[a]



[a] Reagents and conditions: (i) Cl_2POCH_3 (2.5 mol equiv)/(i-Pr)$_2$NEt (7.5 mol equiv)/THF, −78 °C; 2-(2′-iodophenyl)ethanol (3.5 mol equiv), −78 °C to room temperature. (ii) (n-Bu)$_3$SnH (1.4 mol equiv), AIBN (cat)/benzene, reflux, 2 h.

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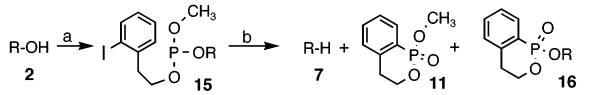
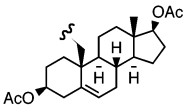
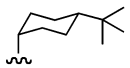
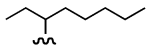
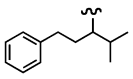
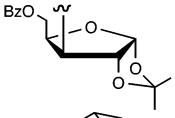
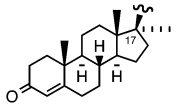
Table 1. Preparation of Phosphites **15** and Radial Deoxygenation of Alcohols **2**



entry	R	phosphite **15** yield (%)[c]	R-H (**7**): yield from **15** (%)	**11** : **16**[d]
1		74	81[c]	5 : 1
2		91	80[e]	5 : 1
3		81	85[e]	7 : 1
4		82	90[c]	10 : 1
5		77	88[c]	1 : 0
6		75	>98[e]	1 : 0
7		85	87[c,f]	1 : 0

[a,b] See conditions i and ii, respectively, in Scheme 3. [c] Yield of isolated, chromatographically pure products. [d] The ratio of the products from the PO−R bond scission and the scission of PO−CH_3 bonds. Estimated by integrations of the corresponding peaks in the ^{1}H and ^{31}P NMR spectra of the crude reaction mixture. [e] Yield estimated by GC−MS using *n*-decane as an internal standard. [f] 17β-Methyl product.

effect the deoxygenation of alcohols, the scope of this newly uncovered reaction was next explored.

As summarized in Table 1, phosphites **15** were accessed under basic conditions in good to excellent yield from the corresponding alcohols **2**, including highly congested alcohols. Radical reduction of all phosphites **15** was equally efficient. The phosphite of a highly congested, neopentyl-type primary alcohol (entry 1) provided the corresponding deoxygenated product in 81% yield, together with a small amount of the phosphonate product **16** from the PO−CH_3 cleavage, as estimated from the ^{1}H and ^{31}P NMR spectra of the crude product. In the reduction of the phosphite derivatives of relatively hindered secondary alcohols (entries 2−5), the undesired β-scission involving the PO−CH_3 bond seems to become less prominent. This marked relative acceleration of the PO−R bond cleavage of the phosphites of these hindered alcohols is likely due to the steric compression effect surrounding the hydroxyl groups of these alcohols. This preference for the cleavage of the PO−R over the PO−CH_3 bonds is even more pronounced in the case of tertiary alcohol derivatives (entries 6 and 7), and virtually no product resulting from the PO−CH_3 cleavage, i.e., **16**, was detected. Significantly, unlike xanthate derivatives of tertiary alcohol,[5] these phospites of tertiary alcohols are thermally stable, even in refluxing benzene.

The diminished contribution of the fragmentation of the PO−CH_3 bond with increasing steric hindrance surrounding the hydroxyl group seems to indicate that the intermediate phosphoranyl radical adopts most likely not a trigonal bipyramidal structure, but other structures such as a quasi-tetrahedral ligand π-electronic structure where the single electron is delocalized throughout the benzene ring.[6,7] 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[8a] 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.

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