Generation of 5- and 6-Membered Ring Radicals by Deoxygenation of Alkoxy Radicals

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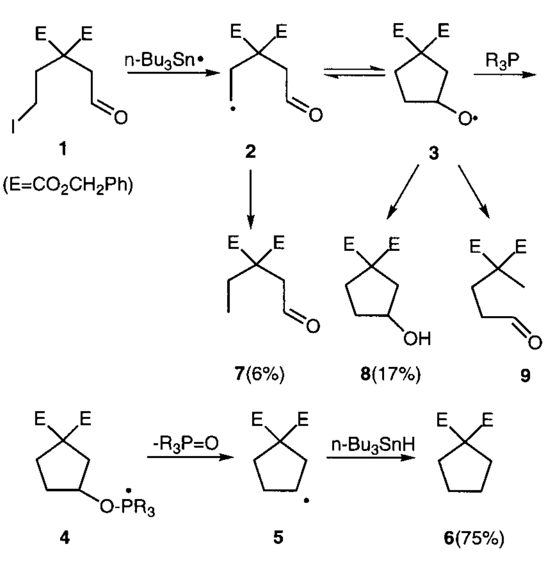
Abstract: A new approach, based on deoxygenation of alkoxyl radicals with triphenylphosphine, for the formation of 5- and 6-membered ring radicals from acyclic radical precursors is described.

Synthetic importance of radical cyclizations has been well recognized in recent years.[1] However, the cyclization pathway is mainly limited to 5-*exo* ring closure along with somewhat less efficient 6-*exo* ring closure due to stereoelectronic and geometric reasons.[2] Furthermore, it is well-known that the formation of 5-membered ring radicals from acyclic radical precursors involving 5-*endo* ring closure is a disfavored process.[3] To solve this problem, we previously reported a reliable method using *N*-aziridinyl imines as radical acceptors.[4] We wish to report an alternative method which is operationally simple because it does not require the conversion of the carbonyl groups into the *N*-aziridinyl imines. Our approach is based on the previously known deoxygenation of alkoxy radicals with organophosphorous(III) compounds (eq 1)[5] and involves an intramolecular addition of an alkyl radical onto the carbonyl group and the subsequent deoxygenation of an alkoxy radical with the phosphorous compound as shown in Scheme 1. In this approach, the phosphorous compound should trap the cyclic alkoxy radical **3** before it would undergo quenching **3** with n-Bu_3SnH and/or well-known β-fragmentation reaction to lead to **9**.[6]

$$RO\bullet \xrightarrow{PR_3} RO\dot{P}R_3 \longrightarrow R\bullet + O{=}PR_3 \qquad (1)$$



Scheme 1

We first examined an alkyl radical addition onto the aldehyde and the subsequent deoxygenation of an alkoxy radical with triphenyl-phosphine to generate a 5-membered ring radical. Since triphenylphosphine reacts with alkyl iodides at an elevated temperature to form alkyltriphenylphosphonium salts, the reaction was carried out at room temperature under photochemically initiated conditions. When a solution of iodoaldehyde **1** with n-Bu_3SnH and triphenylphosphine in degassed benzene (0.05M) was irradiated at 350 nm for 1 h, cyclopentane **6** was isolated in 75% yield along with alcohol **8** (17%) and the direct reduction product **7** (6%). There was no indication of the presence of β-fragmentation product **9.** Among several phosphorous compounds tested in deoxygenation of alkoxy radicals, triphenylphosphine gave the best result and triethylphosphite was similarly effective as shown in Table 1. However, tri-n-butylphosphine was totally ineffective, although tri-n-butylphosphine would be more reactive than triphenylphosphine toward alkoxy radicals. Apparently, α-fragmentation must occur exclusively because the ejection of an alkyl radical from phosphine would be a facile process.[7] Furthermore, it is noteworthy that the addition of an excess amount of phosphine (5 equiv) did not improve the yield and the remaining reactions were carried out with 2 equiv of triphenylphosphine.[8]

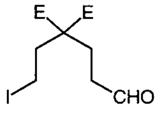
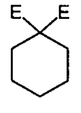
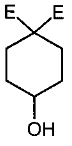
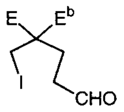
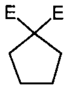
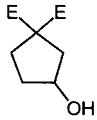
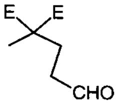
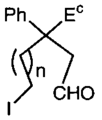
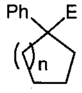
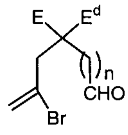
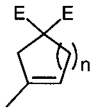
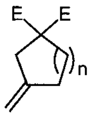
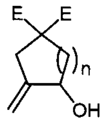
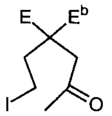
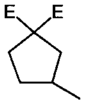
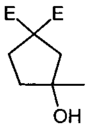
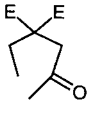
Table 1. Deoxygenation with organophosphorus compounds(III)

R_3P	Products(%)		
	6	7	8
PPh_3 (2 equiv)	75	6	17
PPh_3 (5 equiv)	76	5	15
PPh_3 (10 equiv)	76	5	16
PBu_3 (5 equiv)	-	-	65
$P(OEt)_3$ (2 equiv)	59	-	21
$P(OEt)_3$ (5 equiv)	60	4	4

Table 2 summarizes some experimental results and illustrates the efficiency and the scope of the present method. Radical reactions with **10** and **11** under the similar conditions gave somewhat lower yields. In the case of **12a** and **12b**, somewhat surprisingly, only the desired cyclopentane and cyclohexane derivatives were isolated without the formation of any side products. Vinyl bromide could be utilized as a radical precursor. When vinyl bromide **13a** was subjected to the standard radical condition, a mixture of cyclopentene derivatives was obtained in 68% yield in a ratio of 10:1 along with an alcohol (7%). A similar result was also obtained with **13b**. However, we found that the use of a ketone as a radical acceptor was unsuccessful in the present approach. Thus, treatment of iodoketone **14** with n-Bu_3SnH (1.2 equiv) and triphenylphosphine (2 equiv) in benzene (0.05M) at 350 nm for 1.5 h afforded the direct reduction product (70%) as a major product along with a small amount of the desired methylcyclopentane (17%).

Tandem radical cyclizations were briefly studied under the similar conditions. When **15** was subjected to the standard condition, **16** was isolated in 72% yield after two consecutive radical cyclizations and the subsequent deoxygenation (eq 2). Similar results were also obtained with **17** and **18**, demonstrating the efficiency of deoxygenation reaction by triphenylphosphine (eq 3 and 4). We also examined the feasibility of the cyclization-deoxygenation-intermolecular addition approach which would demonstrate the formation of two carbon-carbon bonds in succession at the same carbon.[9] When iodoaldehyde **19** was treated with acrylonitrile (5 equiv) and Bu_3SnH in the presence of triphenylphosphine (2 equiv) in benzene at 350 nm, the desired product **20** was obtained in 55% yield along with cyclization and deoxygenation

Table 2. Radical cyclization and deoxygenation[a]

substrate	time(h)	product (%)		
 **10**	3	 54%	 19%	
 **11**	1.5	 52%	 5%	 27%
 **12a** n= 1	1.5	 90%		
12b n=2	3	60%		
 **13a** n=1	6	 62%	 6%	 7%
13b n=2	6	45%	6%	16%
 **14**	1.5	 17%	 4%	 70%

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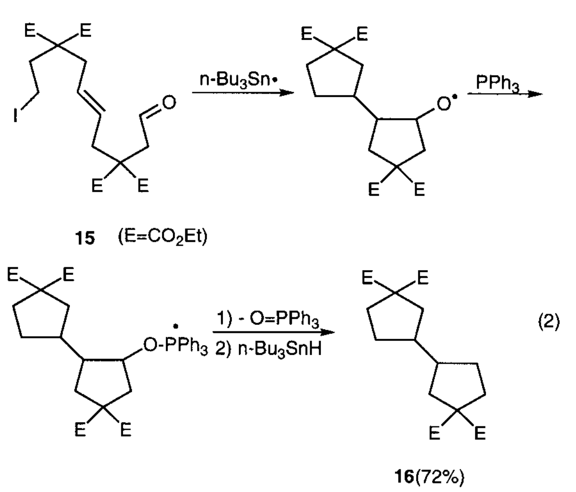
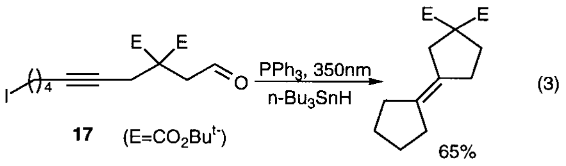
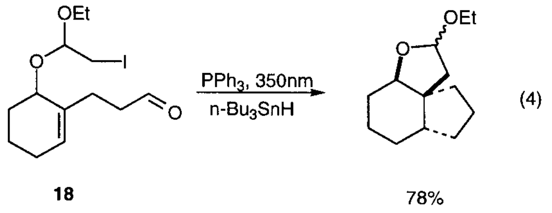
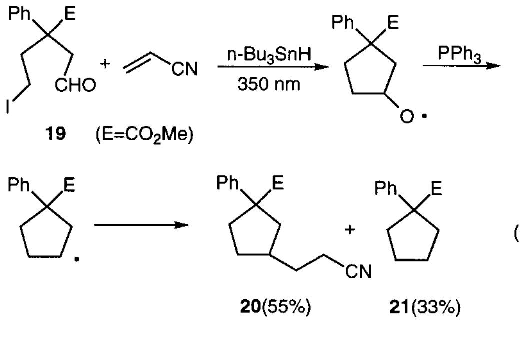
[a] The reaction was carried out with PPh_3 (2 equiv) in benzene (0.05 M in n-Bu_3SnH)[b] $E=CO_2CH_2Ph$ [c] $E=CO_2Me$ [d] $E=CO_2Et$



product **21** (33%) (eq 5). The present reaction demonstrates two consecutive carbon-carbon bond formations although the efficiency of this approach is not very high.







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(8) A benzene solution (4.8 ml, 0.05 M) of iodide **1** (117 mg, 0.24 mmol), 1.2 equiv of n-Bu_3SnH (71 mg, 0.25 mmol), and

triphenylphosphine (188 mg, 0.48 mmol) was degassed for 20 min, and irradiated at 350 nm for 1 h. Then, the reaction mixture was washed with aqueous KF solution (5 ml) and the aqueous layer was extracted with diethyl ether. The resulting solution was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude product was subjected to silica gel column chromatography (EtOAc/hexane = 1/30) to afford **6** (61 mg, 75%) along with **7** (5 mg, 6%) and **8** (15 mg, 17%). **6:** ^{1}H NMR (200MHz, $CDCl_3$) δ 1.63-1.70 (m, 4H), 2.17-2.24 (m, 4H), 5.09 (s, 4H), 7.26-35 (m, 10H); ^{13}C NMR (50.32MHz, $CDCl_3$) δ 25.41, 34.55, 60.44, 66.92, 127.88, 128.12, 128.45, 135.64, 172.29; IR: 3033, 2958, 2874, 1731, 1455, 1263, 1155 cm^{-1}. **7**: ^{1}H NMR (200MHz, $CDCl_3$) δ 0.77(t, J=7.3 Hz, 3H), 2.10(m, 5H), 3.11(s, 2H), 5.10(s, 4H), 7.28-39(m, 10H), 9.64(s, 1H). **8**: ^{1}H NMR (200MHz, $CDCl_3$) δ 1.77-2.02(m, 4H), 2.27-2.47(m, 4H), 4.37(broad s, 1H), 5.08 (s, 2H), 5.11 (s, 2H), 7.28-40(m, 10H)

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