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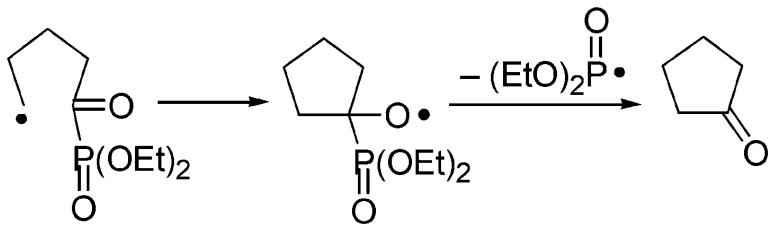

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β-Elimination of a Phosphonate Group from an Alkoxy Radical: An Intramolecular Acylation Approach Using an Acylphosphonate as a Carbonyl Group Acceptor

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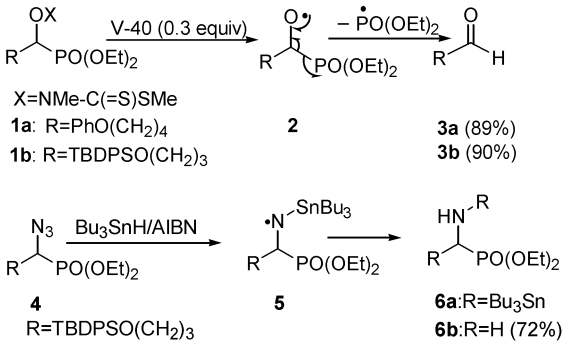
The carbonyl group is one of the central functional groups in organic chemistry and can be readily prepared by treatment of carboxylic acid derivatives with organometallic compounds.[1] However, the radical version of this traditional acylation reaction has not been successful to date because additions of alkyl radicals to C═O bonds are difficult due to their reversibility and the high π-bond strengths of the C═O bonds.[2] Thus, a limited number of carbonyl group radical acceptors is available and includes acyl sulfides, acyl selenides,[3] and acylgermanes[4] in intramolecular acylations.[5]

We have been interested in the possibility of using a phosphonate group as a leaving group in radical reactions. As far as we are aware, there is only one report of β-elimination of a phosphinate group due to aromatization.[6] Since the ease of β-fragmentation generally depends on the nature of the π-bond formed and the strength of the σ-bond broken, the stronger the π-bond formed is, the easier the β-fragmentation would be.[7] Thus, we have investigated an intriguing possibility of β-elimination of a diethyl phosphonate group from an alkoxy radical. When **1a** was reacted with 1,1′-azobis(cyclohexanecarbonitrile) (V-40) as initiator in chlorobenzene at 110 °C for 3 h,[8] aldehyde **3a** was isolated in 89% yield, indicating the facile β-elimination of the phosphonate group from the alkoxy radical for the first time (Scheme 1). A similar result was also obtained with **1b**. However, when azidophosphonate **4** was treated with Bu_3SnH/AIBN in benzene for 2 h,[9] β-elimination of the phosphonate group from the aminyl radical in **5** did not occur probably due to the weak π-bond strength of C═N bonds relative to that of the C═O bonds.

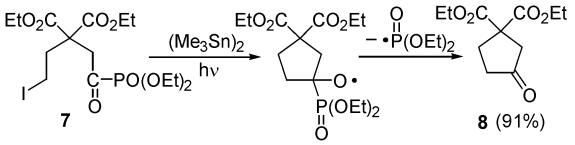
On the basis of our findings, we have studied the feasibility of the use of an acylphosphonate as a carbonyl group radical acceptor (Scheme 2).[10] Acylphosphonates were conveniently prepared by treatment of acid chlorides with triethyl phosphite in dichloromethane at room temperature and were stable to silica gel column chromatographic purification.[11] Radical cyclization of acylphosphonate **7** in the presence of hexamethylditin at 300 nm for 2 h in benzene gave cyclopentanone **8** in 91% yield without the formation of the direct reduction product. The reaction can be carried out in the presence of a catalytic amount of hexamethylditin (0.2 equiv) to afford **8** in 88% yield under similar conditions because initially generated phosphonate radical reacts with an alkyl iodide to generate an alkyl radical.

Table 1 summarizes the experimental results and illustrates the efficiency of the acylphosphonates as the carbonyl group radical acceptor. For most of the cases observed in this study, there was no indication of the presence of the direct reduction product and other side products. It is noteworthy that β-fragmentation of alkoxy radical intermediates did not occur (entry 2). Tandem radical cyclizations work equally well. Not only alkyl radicals but also alkenyl radicals react with acylphosphonates to give cyclopentanone derivatives (entries 4, 5, and 6). An exciting result was obtained

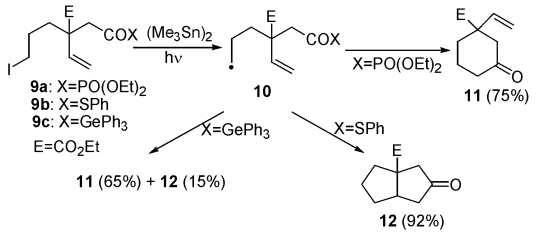
Scheme 1



Scheme 2



with **9**. When **9a** was treated with hexamethylditin (0.2 equiv) at 300 nm for 2 h, gratifyingly, **11** was obtained exclusively, whereas **12** was reported to be a sole product from radical reaction of acyl sulfide **9b**.[3] Apparently, 6-*exo* ring closure to the acylphosphonate is much faster than 5-*exo* ring closure to the C═C bond. To strengthen the efficiency of the acylphosphonate, a comparative experiment was carried out with acylgermane **9c**. When **9c** was irradiated in the presence of hexamethylditin (0.2 equiv) in benzene at 300 nm for 3 h, a 65:15 mixture of **11** and **12** was isolated, indicating higher reactivity of the acylphosphonate relative to that of the acylgermane as the carbonyl group radical acceptor.



On the basis of highly efficient and fast addition of the alkyl radical to the acylphosphonate, we next studied sequential radical reactions involving intermolecular radical addition and cyclization (Scheme 3). This approach provides a ready access to β-functionalized cyclopentanones.[13] Addition of phenylsulfanyl radical and phenylsulfonyl radical to an alkenyl group was followed by cyclization to afford **15** along with generation of diethyl phospho-

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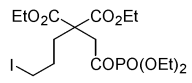
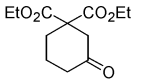
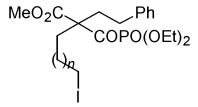
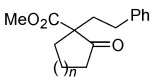
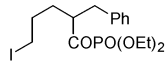
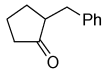
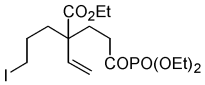
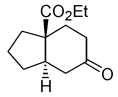
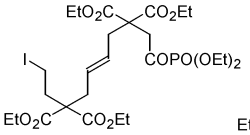
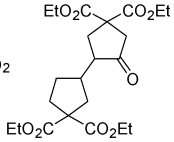
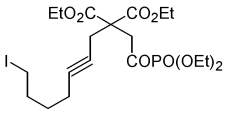
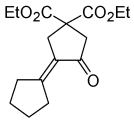
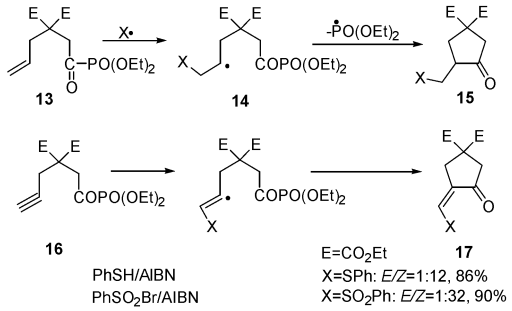
Table 1. Radical Cyclization of Acylphosphonates[a]

entry	substrate	product	yield, %[b]
1			71 (82)[c]
2			*n*=1, 61 *n*=2, 69
3			72
4			69[d]
5			79
6			77

[a] The reaction was carried out with 0.2 equiv of $(Me_3Sn)_2$ in benzene at 300 nm for 2 h. [b] The yield was not optimized. [c] 1.1 equiv of $(Me_3Sn)_2$. [d] Reference 12.

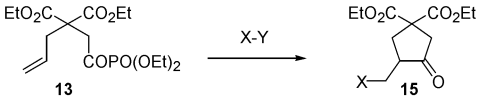
Scheme 3



nate radical for the chain propagation. Similarly, various electrophilic alkyl radicals from activated olefins bearing α-electron-withdrawing groups react smoothly with **13** under tin-catalyzed condition to yield **15** in high yields (Table 2). Apparently, the fast addition of the alkyl radical to the acylphosphonate obviates the problem of quenching of radical intermediate **14** prior to the cyclization. Furthermore, similar results were obtained with alkynylacylphosphonate **16**.

In conclusion, we have shown the facile β-elimination of a phosphonate group from an alkoxy radical and its application to intramolecular acylation approach, in which we demonstrated that

Table 2. Radical Addition and Cyclization of Acylphosphonates



X–Y	condition[a]	time, h	yield, %
PhS−H	A	10	89
$(TMS)_3Si-H$	A	2	75
$PhSO_2-Br$	A	2	90
C_6F_{13}-I	B	5	85
$EtOOCCH_2$-I	B	5	78
$EtOOCCH_2-SC(=S)OEt$	B	5	75
$PhSO_2CH_2$-I	B	5	72
$NCCH_2$-I	B	5	73

[a] Method A: AIBN, C_6H_6, reflux. Method B: 0.2 equiv of $(Me_3Sn)_2$, C_6H_6, $h\nu = 300$ nm.

the acylphosphonates are highly efficient carbonyl group radical acceptors and more reactive than previously known acyl sulfides and acylgermanes.

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Supporting Information Available: Typical experimental procedures and spectral data for products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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