Radical cyclization of thio- and seleno-esters—an intramolecular acylation approach

Sunggak Kim* and Sang Yong Jon

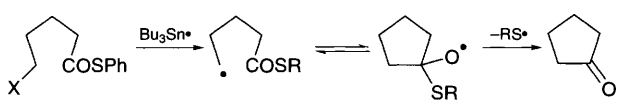
Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

Both thio- and seleno-esters are utilized as carbonyl equivalent radical acceptors in radical cyclizations, where selenoesters are more efficient than thioesters due to the better leaving ability of the phenylseleno group.

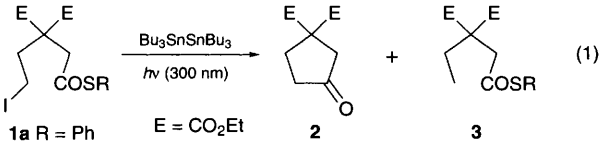
Acylation is one of the most important and fundamental reactions in organic chemistry and is normally achieved by reaction either with carboxylic acid derivatives and organometallic compounds or with masked acyl anions and alkyl halides.[1] Free radical mediated acylation reactions have not been well studied[2,3] 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.[4] The use of a nitrile as a carbonyl equivalent was previously reported[5] but its effectiveness seems to be somewhat limited due to the tendency of facile β-fragmentation of an iminyl radical.[6] Furthermore, an acylgermane has been utilized as a radical acceptor to prepare a cyclic ketone in radical cyclizations.[7] We have examined the feasibility of using a thioester as an acylating agent.

The radical reaction of thioesters was studied to determine the mechanisms of coenzyme B_{12} promoted rearrangements and free radical rearrangements involving 1,2-migration of a thioester group were reported previously.[8] However, as far as we are aware, the use of a thioester group as a carbonyl equivalent radical acceptor has not been reported. Here we report a free radical-mediated intramolecular acylation approach using a thioester group and a selenoester group as a radical acceptor. Our approach involves intramolecular addition of an alkyl radical to a thioester group and subsequent β-elimination of RS radical which reacts with bis(tributyltin) to propagate a chain, Scheme 1. Although the cyclization step would be relatively slow and reversible, β-elimination of RS radical should be irreversible, thereby shifting the equilibrium to the desired direction.

A solution of **1a** and $Bu_3SnSnBu_3$ (1.1 equiv.) in benzene was irradiated at 300 nm.[9] After 2 h the reaction was complete and yielded the cyclopentanone **2** in 87% yield along with the direct reduction product **3** in 11% yield, eqn. (1). However, the use of *S*-butyl thioester **1b** yielded the direct reduction product as a major product (45%), indicating that *S*-phenyl thioesters are better radical acceptors than *S*-alkyl thioesters towards alkyl radicals. Thermal initiation with AIBN was also investigated with **1a**. However, the reaction was incomplete even after 12 h and the yield was considerably lower (60%). Therefore the remaining reactions were carried out with *S*-phenyl thioesters under photochemically initiated conditions.



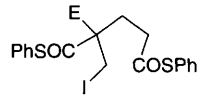
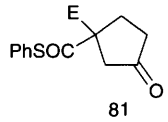
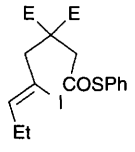
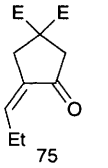
Scheme 1

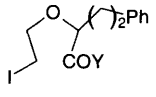


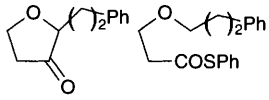
1a R = Ph, **b** R = Bu^n — **2**: 87%, 31% — **3**: 11%, 45%

Table 1 summarizes the experimental results and illustrates the efficiency and scope of the present method. For most of the cases observed with thioesters, considerable amounts of the direct reduction products were isolated and the 6-*exo* cyclization (entries 2 and 6) gave more reduction products than the 5-*exo* cyclization. In competition between 5-*exo* cyclization and 1,2-migration of a thioester group (entry 3), the 5-*exo* cyclization took place exclusively. It is also noteworthy that β-elimination of the phenylsulfanyl group competed with β-cleavage of the C–C bond (entry 8), indicative of the slow rate of β-elimination of the phenylsulfanyl group. Although selenoesters have been only utilized as precursors of acyl radicals,[10] we have examined the feasibility of using selenoesters as radical

Table 1 Radical cyclization of thioesters and selenoesters

Entry	Substrates[a]	*t*/h	Products and yield[b] (%)
1	*n* = 1, X = Br	2	85(14)
2	*n* = 2, X = I	3	46(33)
3		3	 81
4	*n* = 1, Y = SPh		55(28)
5	*n* = 1, Y = SePh	2	80(4)
6	*n* = 2, Y = SPh		46(33)
7	*n* = 2, Y = SePh	2	77(6)
8	Y = SPh	4	51(19)
9	Y = SePh	1.5	80(13)
10		3	 75

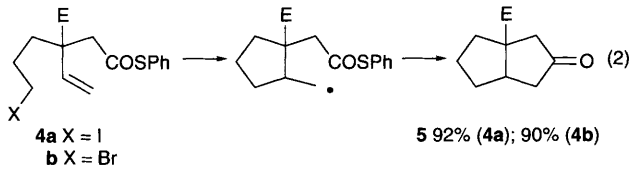




[a] E = CO_2Et. [b] The yield refers to the isolated yield. The numbers in the parentheses indicates the direct reduction products.

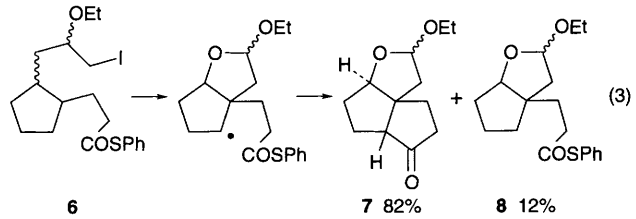
acceptors and we also conceived that β-elimination of the phenylseleno group would be much faster than that of the phenylsulfanyl group, thus providing more cyclized products. As expected, the use of phenyl selenoesters reduced the direct reduction products considerably (entries 5, 7 and 9) and obviated the problem of β-cleavage of the C–C bond (entry 9). A vinyl radical underwent clean cyclization to a thioester (entry 10).

We next examined sequential radical cyclizations, eqn. (2). Treatment of **4a** with $Bu_3SnSnBu_3$ (1.1 equiv.) in benzene at 300 nm for 3 h afforded the bicyclic ketone **5** in 92% yield, demonstrating the effectiveness of a thioester group as a radical acceptor. The bromide **4b** was equally effective in radical cyclization. The similar result was also obtained with compound **6**, although the second cyclization step was slightly less efficient than the first cyclization step, eqn. (3).



4a X = I
b X = Br

5 92% (**4a**); 90% (**4b**)



6 **7** 82% **8** 12%

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