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Construction of Tetrahydrofuran-3-ones from Readily Available Organochalcogen Precursors via Radical Carbonylation/ Reductive Cyclization

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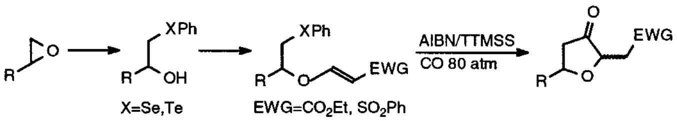
ABSTRACT



β-Hydroxyalkyl aryl chalcogenides, readily available by regioselective ring-opening of epoxides with nucleophilic benzeneselenolate or tellurolate, were *O*-alkylated by treatment with ethyl propiolate or (*E*)-1,2-bis(phenylsulfonyl)ethylene. Subsequent carbonylation/reductive cyclization in the presence of AIBN/TTMSS and carbon monoxide (80 atm) afforded tetrahydrofuran-3-ones in moderate to good yields.

As a result of recent interest in radical-mediated synthesis, acyl radical chemistry has also seen a renaissance.[1] Acyl radicals take part in a large variety of inter- and intramolecular reactions and are therefore useful synthetic intermediates.[2] These species are commonly generated by homolysis of an acyl−X bond, where X could be hydrogen, halogen, chalcogen, or a metal. Since most of these derivatives suffer from certain shortcomings in radical processes, i.e., inefficient chain-transfer, over-reduction, or poor reactivity toward stannyl or silyl radicals, selenol esters have become the most versatile precursors for acyl radicals.[3] As demonstrated by Ryu and co-workers, acyl radicals can also be readily formed by reaction of alkyl radicals with carbon monoxide.[1,4,5] These carbonylation reactions are commonly performed as one-pot reactions with 60−80 atm of CO, conditions which can easily be obtained by using an ordinary autoclave. Primary, secondary, and tertiary radicals can be efficiently carbonylated and further transformed in more or less elaborate ways into carbonyl derivatives such as aldehydes,[6] ketones,[7] esters,[8] lactones,[9] thiolactones,[10] amides,[11]

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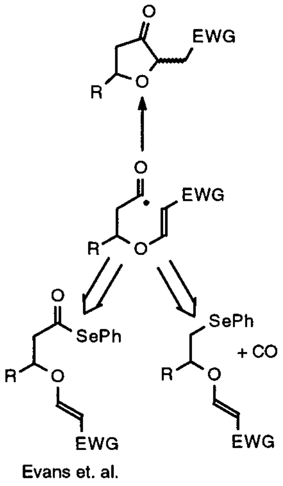
lactams,[12] and acyl selenides.[13] Atom or group transfer, inter- or intramolecular radical addition, cascade reactions, radical translocation, one-electron oxidation, or ionic chemistry are noteworthy features of these transformations.

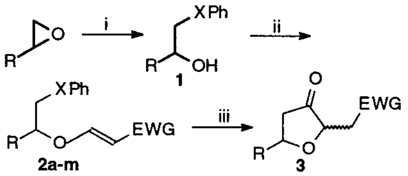
It occurred to us that radical carbonylation/reductive cyclization could provide easy access to 2,5-disubstituted tetrahydrofuran-3-ones from readily available organochalcogen precursors. Evans and co-workers have already shown that cyclic ethers can be efficiently prepared by using intramolecular acyl radical cyclizations (Scheme 1).[14,15] By generating acyl radicals directly from alkyl radicals and carbon monoxide (Scheme 1), one could approach these systems in a different way, using more readily available starting materials. Also, radical decarbonylation, a sometimes unwanted side-reaction, could be suppressed.[4,14a,b]

Scheme 1



Some time ago, we showed that epoxides can be regioselectively ring-opened by benzeneselenolate or benzenetellurolate to furnish β-hydroxyalkyl phenyl chalcogenides **1**.[16] For preparation of 2,5-disubstituted tetrahydrofuran-3-ones by radical carbonylation/reductive cyclization, β-hydroxyalkyl phenyl selenides **1** were allowed to undergo hetero-Michael addition[14a−c,15b,17] to ethyl propiolate or to act as nucleophiles in the vinylogous substitution of (*E*)-1,2-bis(phenylsulfonyl)ethylene[14d,15a] (Scheme 2).

Scheme 2[a]



[a] (i) $(PhSe)_2$ or $(ArTe)_2$, $NaBH_4$; (ii) ethyl propiolate, NMM or (*E*)-1,2-bis(phenylsulfonyl)ethylene, NaH; (iii) AIBN, TTMSS, CO 80 atm.

The *O*-vinylation proceeded smoothly at room temperature to give radical precursors **2a**−**k** in 64−95% isolated yields as pure *E*-isomers (Table 1). However, attempts to prepare a tertiary alcohol radical precursor **2l** failed (Table 1, entry 12).

Carbonylation/radical cyclization was conducted in an autoclave equipped with a stirring rod. To find proper reaction conditions, selenide **2a** was carbonylated/cyclized under various conditions (Table 2). The use of tri-*n*-butyltin hydride as a hydrogen atom donor was found to cause formation of substantial amounts of reduced product **4**. Better results were obtained using tris(trimethylsilyl)silane (TTMSS). With carbon monoxide at 80 atm, an 86% yield of compound **3a** as a 9:1 mixture of cis and trans isomers was obtained. At lower pressures (60 atm), reduction of the starting material again started to become a significant side reaction. Tri-*n*-butylgermane was also tried as a hydrogen atom donor, but found inferior to TTMSS. Thus, subsequent carbonylation/reductive cyclizations were carried out using TTMSS as a hydrogen atom donor and CO at 80 atm (Table 1).

As shown in Table 1 (entries 1−4), organotellurium precursors **2b** and **2d** performed almost as well as their organoselenium counterparts in the chemistry developed. The unexpectedly low yield of compound **3c** was a consequence of a competing 1,5 hydrogen atom shift/6-*exo*-cyclization (Scheme 3). This gave rise to byproduct **5** which was isolated in 32% yield starting from compound **2c** and 30% starting from **2d**. Only one diastereomer of dioxan **5** was isolated, with all three substituents occupying equatorial positions. In a separate experiment carried out in the absence of CO, the dioxane derivative **5** was isolated in 82% yield along with 3% reduced starting material.

It is also noteworthy that the benzylic radical formed from compound **2e** (Table 1, entry 5) failed to undergo carbonylation/5-*exo*-cyclization. Only reduced starting material was formed in 56% yield. However, this is in accord with previous observations that carbonylated stabilized radicals (benzylic, allylic, tertiary) decarbonylate more rapidly than other acyl radicals.[1] Carbonylation/cyclization of radical precursors **2f**−**i** afforded 2,5-disubstituted tetrahydrofuran-3-ones in moderate to good yields. The β-hydroxyalkyl phenyl selenides originating from 1,2-disubstituted epoxides (Table 1, entries 10−11) furnished 2,4,5-trisubstituted tet-

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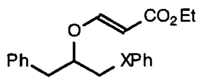
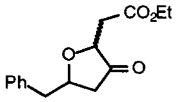
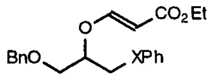
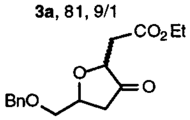
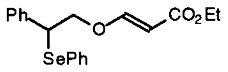
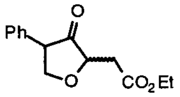
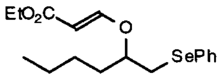
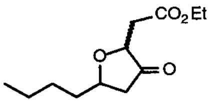
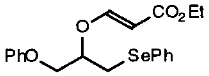
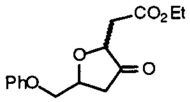
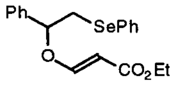
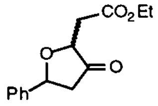
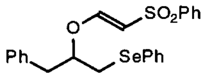
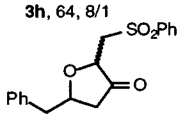
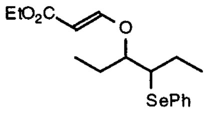
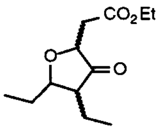
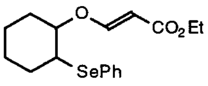
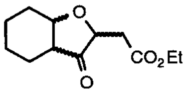
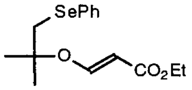
Table 1. Radical Precursors and Their Conversion to Tetrahydrofuran-3-ones

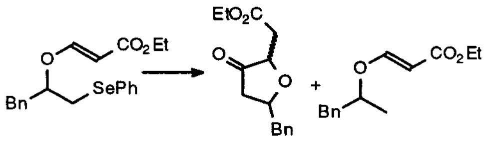
Entry	Radical precursor, compound no., yield[a]	Tetrahydrofuran-3-one, compound no., yield[a], *cis*/*trans*-ratio	Yield[a] of reduced uncyclized material
			
1	**2a**, X = Se, 95	**3a**, 86, 9/1	
2	**2b**, X = Te, 64	**3a**, 81, 9/1	
			
3	**2c**, X = Se, 83	**3c**, 42, 7/1	
4	**2d**, X = Te, 80	**3c**, 40, 7/1	
5	 **2e**, 89	 **3e**, 0	56
6	 **2f**, 76	 **3f**, 77, 7/1	10
7	 **2g**, 85	 **3g**, 82, 4/1	6
8	 **2h**, 83	 **3h**, 64, 8/1	14
9	 **2i**, 79	 **3i**, 59, 9/1	
10	 **2j**, 64	 **3j**, 65, [b]	
11	 **2k**, 86	 **3k**, 78, [b]	
12	 **2l**, 0		

[a] Isolated yield in percent. [b] Inseparable mixture of diastereomers.

rahydrofuran-3-ones as inseparable mixtures of diastereomers. It seems that carbonylation of the secondary alkyl radical produces both of the possible (cis/trans) diastereomeric acyl radicals, which then undergo 5-*exo*-cyclization.

The stereochemistry of the 2,5-disubstituted tetrahydrofuran-3-ones prepared was assigned by using 2D NOESY experiments. A 1,3 NOE was always seen for the cis isomer. The selective formation of *cis*-2,5-disubstituted tetrahydrofuran-3-ones follows from the Beckwith−Houk rules for ring closure, assuming that the 2,5-substituents are both pseudoequatorial in the chairlike transition state.[18] Some attempts were also made to epimerise the diastereomeric mixture of cis/trans 2,5-disubstituted tetrahydrofuran-3-ones. By treat-

Table 2. Optimization of Carbonylation/Reductive Cyclization



2a **3a** **4**

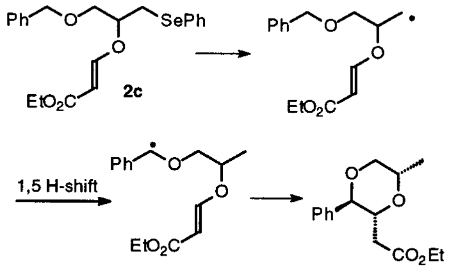
	P CO (atm)	Yield of **3a** (%)[a]	Yield of **4** (%)[a]
n-Bu_3SnH	60	64	15
TTMSS	60	81	6
TTMSS	80	86	0
n-Bu_3GeH	80	86	6

[a] Isolated yield.

ment of compound **3a** with 0.1 equiv of DBU in refluxing benzene, the cis/trans ratio could not be improved more than to 1:2.

In conclusion, we have shown that substituted tetrahydrofuran-3-ones are easily prepared from *O*-vinylated-β-hydroxyalkyl phenyl chalcogenides via carbonylation/reductive cyclization. As compared with the cyclization of acyl radicals as reported by Evans,[14b,c] cyclization yields were usually somewhat lower. However, considering the availability of the organoselenium radical precursors from epoxides, the methodology reported herein would seem useful for the construction of a variety of cyclic ethers.

Scheme 3



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Supporting Information Available: Experimental procedures and characterization data for new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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