Communications

Stereoselective Construction of Cyclic Ethers *via* Intramolecular Acyl Radical Cyclizations: A Practical Solution to Decarbonylation

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Cyclic ether containing natural products represent important synthetic targets owing to their unique structural and biological properties.[1] The development of new methodology for the synthesis of this ubiquitous class of compounds has been the focus of extensive investigation for the last 20 years. However, the development of new and general methods capable of accessing this class of compounds continues to dominate this area of investigation.[2] A number of radical methods[3−5] have recently been developed for the stereoselective synthesis of cyclic ethers. Methods that utilize acyl radicals[6] have, however, not been forthcoming. In this paper, we describe the first example of the intramolecular addition of an acyl radical to a vinylogous carbonate for the efficient and stereoselective construction of 5-, 6-, and 7-membered cyclic ethers (eq 1).[7]

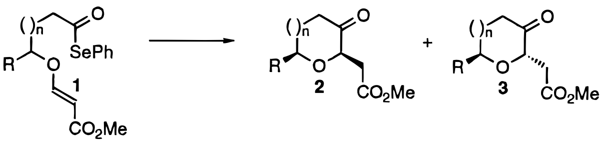

Table 1 summarizes the results for the intramolecular acyl radical cyclizations. Treatment of the acyl selenides **1a−c** with triphenyltin hydride and triethylborane at reflux, in the presence of air, furnished the 2,5-disubstituted tetrahydrofuran-3-ones **2**/**3a−c** in 93−97% yield with high *cis*-diastereoselectivity (Table 1, entries 1−3). The stereochemical outcome of these cyclizations is fully in accord with the Beckwith transition state model, which has been used extensively to predict and rationalize the outcome of 5-hexenyl-type radical cyclizations.[8] The model predicts that the favored transition state I ($n = 0$) has an overall chairlike conformation in which the alkyl substituent is pseudoequatorial and the vinyl ether *s-trans* (Figure 1).[9] The disfavored transition state has a boatlike conformation in which the vinyl ether is *s-cis*.

The synthesis of tetrahydropyran-3-ones was initiated by treating the acyl selenide **1d** under analogous conditions to those described above to afford the 2,6-disubstituted tetrahydropyran-3-ones **2**/**3d** in modest yield with poor diastereoselectivity (Table 1, entry 4). The major diastereoisomer was assigned as the *cis*-2,6-disubstituted tetrahydropyran-3-one **2d** from NOE studies. The modest yield was attributed to competitive reduction to afford the aldehyde **4**. This is presumably the result of a slower rate of cyclization for the 6-*exo*- *vs* 5-*exo*-trigonal cyclization.[3] Reversion to the more classical syringe pump addition of tributyltin hydride to the acyl selenide **1d** avoided reduction and furnished the cyclic ethers **2**/**3d** in excellent yield (Table 1, entry 4). The lower diastereoselectivity was attributed to the disfavored transition state II ($n = 1$), in which the vinyl ether adopts an *s-cis* orientation in the transition state leading to the product (Figure 1).[9] Nonetheless, treatment of the diastereomeric mixture **2**/**3d** with a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in refluxing benzene improved the diastereoselectivity (11−19:1) in 95% yield.

In order to enhance the formation of the *cis*-diastereoisomer, the effect of temperature on the diastereoselectivity of the cyclization was examined. Treatment of the acyl selenides **1d−f** with tris(trimethylsilyl)silane and triethylborane at room temperature, in the presence of air, furnished the 2,6-disubstituted tetrahydropyran-3-ones **2**/**3d−f** in 85−94% yield as a 5.7:1 mixture of diastereoisomers (Table 1, entries 4−6).[10] Indeed, the ratio could be further improved by carrying out the reaction at even lower temperature. Treatment of the acyl selenide **1d** with tris(trimethylsilyl)silane and tri-

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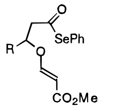
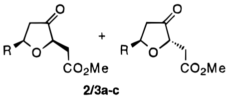
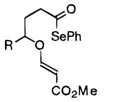
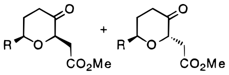
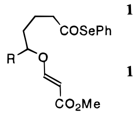
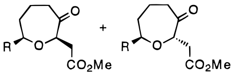
Table 1. Intramolecular Acyl Radical Cyclization of the Acyl Selenides[13] 1a−i

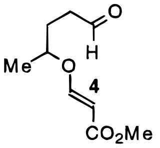
Entry	Acyl Selenide **1**		Cyclic Ether **2/3**[a]	Method[b]	Ratio of **2** : **3**[c]	Yield (%)[d]
1		**1a** R = Me	 **2/3a-c**	A	10 : 1	97
2		**1b** R = Ph		A	≥19 : 1	90
3		**1c** R = ^{i}Pr		A	17 : 1	94
4		**1d** R = Me	 **2/3d-f**	A	3.5 : 1	63
				B	3.5 : 1	92
				C	5.7 : 1	94
				D	7.1 : 1	94
5		**1e** R = Ph		C	5.7 : 1	85
6		**1f** R = ^{i}Pr		C	5.7 : 1	94
7		**1g** R = Me	 **2/3g-i**	B	10 : 1	70
				C	19 : 1	89
8		**1h** R = Ph		B	≥19 : 1	48
				C	≥19 : 1	80
9		**1i** R = ^{i}Pr		C	≥19 : 1	90

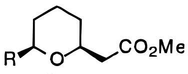
[a] All the cyclizations were carried out on a 1 mmol reaction scale. [b] Method A: Ph_3SnH, Et_3B, PhH, Δ. Method B: $^nBu_3SnH$, AIBN, PhH, Δ. Method C: $(TMS)_3SiH$, Et_3B, PhH, RT. Method D: $(TMS)_3SiH$, Et_3B, PhMe, −20 °C. [c] Ratios of diastereoisomers determined by ^{1}H-NMR integration. [d] Isolated yields.

Figure 1.

ethylborane, at −20 °C in toluene, furnished the tetrahydropyran-3-ones **2**/**3d** in 94% yield as a 7.1:1 mixture of diastereoisomers (Table 1, entry 4). The ability to improve the selectivity in this manner adds an element of control to radical reactions of this nature. The modest diastereoselectivity in this particular cyclization is rather intriguing, especially in view of the fact that the corresponding alkyl radical addition is completely *cis*-selective.[5c] This result suggests that it may be the radical geometry that is responsible for the lower selectivity. Further work is underway to elucidate the reason for the modest diastereoselectivity.

The methodology was also applied to the synthetically more demanding 2,7-disubstituted oxepan-3-ones **2**/**3g**−**i**. Treatment of the acyl selenides **1g**,**h** with tributyltin hydride, delivered *via* syringe pump, and a catalytic amount of AIBN in refluxing benzene afforded the oxepan-3-ones **2**/**3g**,**h** in a 48−70% yield, as a 10 to ≥19:1 mixture of diastereoisomers (Table 1, entries 7 and 8). NOE studies established the major diastereoisomer to be the *cis*-2,7-disubstituted oxepin-3-one **2g**. The modest yields were attributed to decarbonylation of the acyl radical to produce the corresponding alkyl radical, which underwent smooth cyclization to produce the *cis*-2,6-disubstituted tetrahydropyrans **5a** and **5b**. Decarbonylation is an inconvenient side reaction which is often encountered in acyl radical cyclization reactions. This can often be suppressed by employing a high pressure of carbon monoxide.[3e,11] However, the high pressures (~30−75 atm) dictate that a specialized apparatus be employed which limits the practicality of the method. The rate of decarbonylation is known to increase as a function of temperature.[12] Therefore, the formation of the 2,7-disubstituted oxepin-3-ones **2g**−**i** was carried out at lower temperature. Treatment of the acyl selenides **1g**−**i** with tris(trimethylsilyl)silane and triethylborane, in the presence of air, at room temperature afforded the 2,7-disubstituted oxepan-3-ones **2**/**3g**−**i** in 80−90% yield as a ≥19:1 mixture of diastereoisomers (Table 1, entries 7−9).





5a R = Me
5b R = Ph

In order to confirm this result, the reaction was carried out under analogous conditions, at elevated temperature. Treatment of the acyl selenide **1g** with tris(trimethylsilyl)silane and AIBN, in refluxing benzene, afforded the 2,7-disubstituted oxepan-3-ones **2**/**3g** in 65% yield as a 8.5:1 mixture of diastereoisomers and the *cis*-2,6-disubstituted tetrahydropyran **5a** in 24% yield from competitive decarbonylation and *in situ* cyclization.

The excellent regiochemical control in the cyclization reactions described herein is presumably the result of the intramolecular addition of a nucleophilic acyl radical to the LUMO of the vinylogous carbonate.[14] The stereocontrol is the result of the favored transition state I (n = 0, 1, and 2) having the alkyl substituent pseudoequatorial with the vinyl ether *s-trans* to presumably alleviate $A^{1,3}$-type allylic strain in the transition state leading to the product (Figure 1).[9]

In conclusion, we have demonstrated the first example of the intramolecular addition of an acyl radical to a vinylogous carbonate for the efficient and stereoselective synthesis of 5-, 6-, and 7-membered cyclic ethers. *The tris(trimethylsilyl)silane/triethylborane reagent combination is a particularly attractive method for both improving stereocontrol and suppressing decarbonylation.*

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Supporting Information Available: Cyclization procedures and characterization for compounds **1**−**2a**−**i**, **4**, and **5a/b** (10 pages).

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(14) The LUMO of an acrylate and a vinyl ether is known to have larger coefficients at the β- and α-carbon, respectively, thus reinforcing each other in a β-alkoxyacrylate. See: Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: New York, 1977; p 186.