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SYNTHESIS OF OXACYCLIC CARBOXYLIC ESTERS THROUGH RING CLOSURE OF α-ALKOXY ESTER FREE RADICALS

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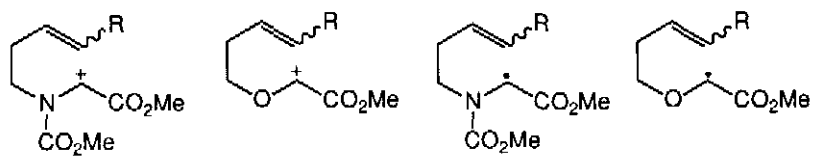
Summary: Cyclizations of 1-methoxycarbonyl-2-oxa-5-hexenyl (and related) radical intermediates, generated from phenylthio precursors, proceed in good yields and mainly lead to substituted 2-tetrahydrofurancarboxylic esters.

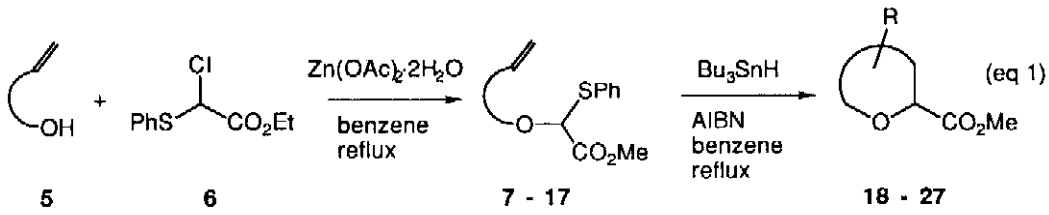
In recent years the cationic species **1** and **2**, characterized by the presence of a *stabilizing* (carbamate nitrogen and ether oxygen, respectively) and a *destabilizing* (methoxycarbonyl) substituent directly bonded to the positive carbon, have proven to be useful synthetic intermediates, which readily cyclize to mainly six-membered aza- and oxacyclic carboxylic esters.[1,2] The corresponding radical species **3** and **4**, on the contrary, are *stabilized* by both the heteroatom and the ester substituent. It has been suggested, that the presence of both an electron-donating and an electron-withdrawing substituent has a synergistic effect on radical stability, the so-called capto-dative effect.[3] One may thus wonder whether **3** and **4** are reactive enough to cyclize onto an unactivated alkene. We have recently shown that **3** indeed cyclizes surprisingly smoothly to mainly proline derivatives, and thus nicely complements the cationic variant.[4] In this paper we show that **4** cyclizes to mainly 2-tetrahydrofurancarboxylic esters, albeit somewhat less readily than ring closure of **3**.



1 **2** **3** **4**

The general reaction sequence is shown in eq 1. Treatment of the unsaturated alcohols **5** with 2-chloro-2-(phenylthio)acetic acid ethyl ester **6**[5] in the presence of zinc acetate dihydrate in refluxing benzene with a Dean Stark trap gave the desired radical precursors **7-17** in about 75% yield in most cases (see Table).[6] The starting alcohols **5** were commercially available except for those leading to **10**,[7] **12**,[8] and **13**.[9] Radical cyclizations were carried out by dropwise addition of a ca. 0.1 M solution of tri-*n*-butyltin hydride (1.5 *equiv*) and 2,2'-*azobisisobutyronitrile* (AIBN; *catalytic amount*) in *benzene to a refluxing ca.* 0.07 M solution of **7-17** in benzene under a nitrogen atmosphere over a period of 6 h. The results of seven 1-methoxycarbonyl-2-oxa-5-hexenyl radicals (from **7-13**), one corresponding 5-hexynyl radical (from **14**), and three corresponding 6-heptenyl radicals (from **15-17**) are detailed in the Table. Most products could be obtained pure by using flash chromatography.[10] Preparative gas chromatography[11] was required for the

separation of the cyclization products from precursors **11** and **14**. This *cis/trans* isomers of **18**, **19**, and **20** could not be separated. In some cases uncyclized reduction products (**28-33**) were isolated.



5 **6** **7 - 17** **18 - 27**

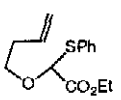
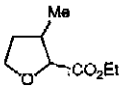
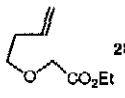
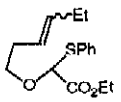
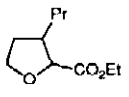
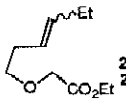
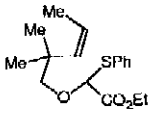
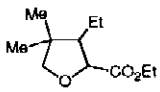
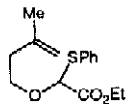
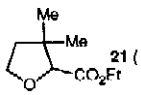
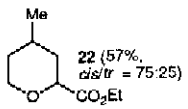
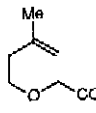
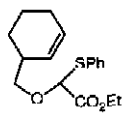
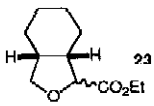
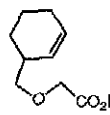
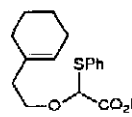
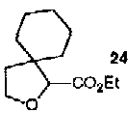
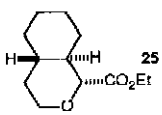
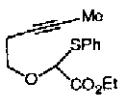
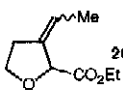
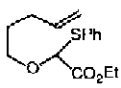
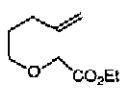
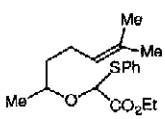
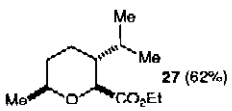
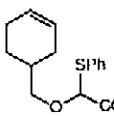
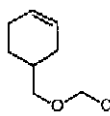
All radical cyclization products were unknown in the literature. The structural and stereochemical assignments were mainly based on ^{1}H and ^{13}C NMR analyses. The ^{1}H NMR signals of the methine hydrogens adjacent to the ester function were most diagnostic, and are given in the Table. The *cis*-2,3-substituted tetrahydrofurancarboxylates always showed a lower field absorbtion (ca. 4.4-4.6) for this hydrogen (see **18-20**, **23**), than the *trans*-compounds (ca. 4.0-4.3). Except for **23**, the *cis*-compounds had larger vicinal coupling constants than the *trans*-systems. These findings were in agreement with results for the 3-vinyl analogue,[2] and the corresponding pyrrolidine systems.[4] The stereochemistry of **23** and **26** was further established by using NOE difference measurements. The vicinal coupling constants of the ester methine hydrogens in the tetrahydropyran systems **22**, **25**, and **27** provided good evidence for their stereochemistry. The methyl esters corresponding to **22** were known compounds.[12] The ring fusion stereochemistry in **25** was based on literature analogy.[4,13]

The results in the Table indicate that cyclization of 2-oxa-5-hexenyl radicals **4** (from precursors **7-13**) proceed in preparatively useful yields. However, comparison with previous results on cyclizations of the nitrogen analogue **3**[4] shows some differences. Firstly, cyclizations of the ether systems seem to be less facile than cyclization of the carbamates. This is illustrated by the formation of 28% of uncyclized reduction product **28** from **7**, while under comparable conditions the analogous carbamate gives only cyclization.[4] Similarly, precursor **17** gives no cyclization at all, whereas the nitrogen analogue provides 29% cyclization product in addition to 54% uncyclized product. Secondly, **4** shows a greater preference for 5-exo cyclization than **3**. We have found earlier that the parent **3** (R = H) gives a 2/1 ratio of exo vs. endo cyclization. The radical from **7** on the other hand gives exclusively exo cyclization. Geometric factors, i.e. the bond angle of an ether oxygen (ca. 110°) vs a carbamate nitrogen (ca. 120°) might be responsible for this difference.[14] Thirdly, there is little preference for the formation of either *trans*- or *cis*-2,3-disubstituted tetrahydrofurans. This is in between the results for 1-substituted 5-hexenyl radical cyclization,[15] which give mainly the *cis*-products, and the nitrogen analogues **3**,[4] producing mostly the *trans*-products. A large 2,3-*cis*-selectivity in tetrahydrofuran formation has been observed in an ionic reaction proceeding via **2**.[2]

The 2-oxa-5-hexynyl radical cyclization from **14** proceeds in excellent yield. On the contrary, the 2-oxa-6-heptenyl radical cyclizes only if a reactive olefin is available as in **16**. Remarkably, the product is formed as a single isomer **27** with all substituents in an equatorial orientation. Precursors **15** and **17** only led to uncyclized reduction products **32** and **33**, respectively.

The preparation of oxygen heterocycles by way of radical cyclization is a topic of high current interest,[16] in particular in the synthesis of lactones.[17] Such cyclizations have been performed via α-alkoxy[16a-c] as well as α-ester[17e-g] radical intermediates. We have now shown that the direct attachment of both these functional groups to the radical carbon still allows synthetically useful ring closure reactions.

Table

radical precursor (yield)[a]	products (isolated yields) cyclized	products (isolated yields) uncyclized	^{1}H NMR data for the ester methine hydrogen (ppm)[b]
 **7** (81%)	 **18** (53%, *cis*/*tr* = 57:43)	 **28** (28%)	*cis*-**18** : 4.39 (d, *J* = 7.8 Hz) *tr*-**18** : obscured
 **8** (*E*, 80%) **9** (*Z*, 79%)	 **19** (77%, *cis*/*tr* = 35:65) **19** (65%, *cis*/*tr* = 54:46)	 **29** (*E*, <2%) **29** (*Z*, 5%)	*cis*-**19** : 4.45 (d, *J* = 7.9 Hz) *tr*-**19** : 4.07 (d, *J* = 5.8 Hz)
 **10** (21%)	 **20** (72%, *cis*/*tr* = 44:56)		*cis*-**20** : 4.62 (d, *J* = 9.4 Hz) *tr*-**20** : 4.15 (d, *J* = 8.5 Hz)
 **11** (71%)	 **21** (15%)  **22** (57%, *cis*/*tr* = 75:25)	 **30** (16%)	**21**: 4.01(s) *cis*-**22** : 3.91(dd, *J* = 11.7, 2.3 Hz) *tr*-**22** : 4.36 (t, *J* = 4.8 Hz)
 **12** (80%)	 **23** (68%, *cis*/*tr* = 53:47)	 **31** (24%)	*cis*-**23** : 4.45 (d, *J* = 5.3 Hz) *tr*-**23** : 4.29 (d, *J* = 6.2 Hz)
 **13** (62%)	 **24** (22%)  **25** (35%)		**24** : 4.20 (s) **25** : 3.57 (d, *J* = 9.9 Hz)
 **14** (77%)	 **26** (88%, *E*/*Z* = 50:50)		**26**(*E*) : 4.75 (t, *J* = 1.7 Hz) **26**(*Z*) : 4.94 (bs)
 **15** (77%)		 **32** (69%)	
 **16** (50%)	 **27** (62%)		**27** : 3.83 (d, *J* =9.9 Hz)
 **17** (66%)		 **33** (64%)	

[a] Isolated yields from the unsaturated alcohol **5**. [b] Solvent $CDCl_3$ for **21**, **22**, **26**, and **27**; C_6D_6 for the remaining compounds.

Obvious applications of the products are the reduction to carbohydrate analogues and the oxidative decarboxylation to lactones.[18]

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