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DIASTEREOSELECTIVE FORMATION OF CYCLIC CARBONATES BY CYCLIZATION OF ALKENYLOXYCARBONYLOXY RADICALS

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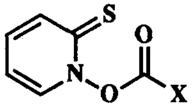
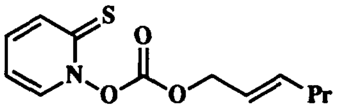
Abstract: The alkenyloxycarbonyloxy radical (**8**) derived from *trans*-hex-2-en-1-ol via the *N*-hydroxypyridine-2-thione carbonate (**4**) undergoes fast ($k_c > 4.0 \times 10^8\ s^{-1}$ at 80°C) cyclization exclusively in the *exo* mode to give a cyclic radical (**9**) which is converted into products (**6**,**7**) by diastereoselective S_H2 reactions; radicals derived from homoallylic alcohols behave similarly.

Since Barton[1] first showed that *N*-acyloxypyridine-2-thiones (**1**) undergo chain decomposition via the generation and subsequent decarboxylation of acyloxy radicals, $RCO_2\bullet$, these compounds have assumed importance in synthesis as precursors of carbon centred radicals.[2] Recently, Newcomb reported that the related carbamates (**2**) behave similarly and afford aminyl radicals (or aminium cation-radicals in the presence of protic or Lewis acids) by decarboxylation of the initially formed $R_2NCO_2\bullet$ radicals.[3] However, attempts in these laboratories to use the corresponding carbonates (**3**) as sources of alkoxy radicals were unsuccessful,[4] because the decarboxylation of $ROCO_2\bullet$ is too slow to compete effectively with intermolecular reactions.[5,6] Recently it has been shown that $ROCO_2\bullet$ radicals can undertake intermolecular addition to olefins.[6,7] We now report that such radicals containing a suitably disposed double bond undergo fast, highly regioselective, *exo* ring closure, and that in some cases the cyclized radicals are converted into the final products by diastereoselective S_H2 processes.



1, X = R
2, X = NR_2
3, X = OR



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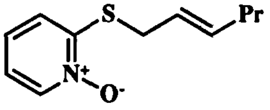
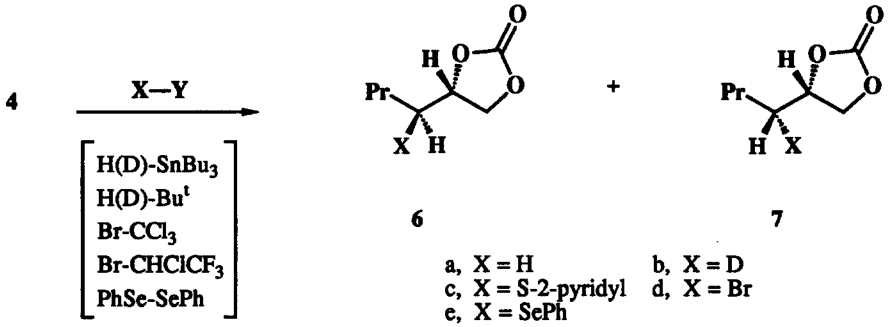


5

A number of exploratory experiments were conducted with the carbonate **4**[8] which was obained in 79% yield after chromatography by consecutive treatment of *trans*-hex-2-en-l-ol with phosgene and with the sodium salt of 2-mercaptopyridine-*N*-oxide.[9] Unfortunately, the carbonate **4** undergoes slow but quantitative conversion into the *N*-oxide, **5**,[10] on storage and must therefore be freshly prepared before use. The mechanism of the formation of **5** from **4** by what appears to be a decarboxylative rearrangement is currently under investigation.

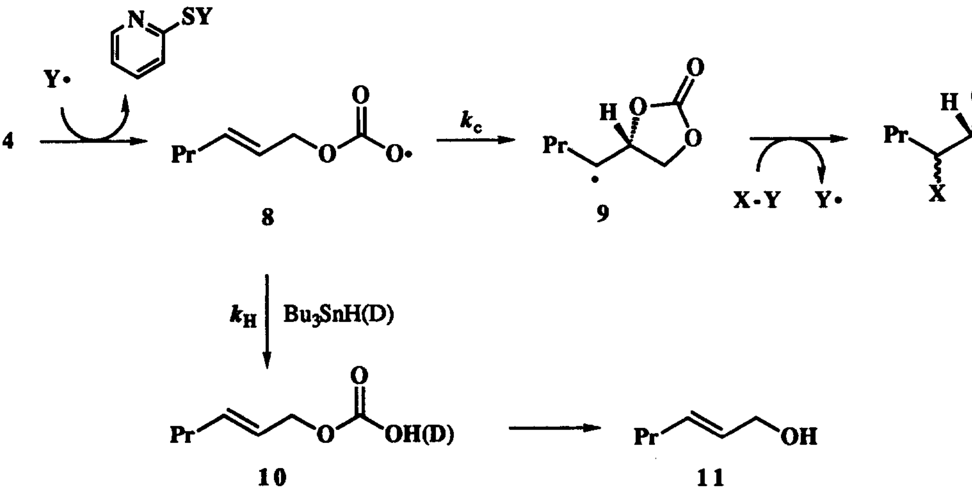
When **4** was slowly added to a refluxing solution of *tert*-butyl mercaptan in benzene the cyclic carbonate **6a** was isolated by chromatography in 65% yield. A similar result was obtained when *tert*-BuSD or Bu_3SnD was used as the chain carrier, and in these cases it was possible to detect by ^{2}H nmr the formation of the diastereoisomers, **6b** and **7b** in the ratio of 1.6:1. The assignment of stereochemistry was confirmed by an independent synthesis of **6b**.[11]



6 **7**

a, X = H b, X = D
c, X = S-2-pyridyl d, X = Br
e, X = SePh

Irradiation of solutions of **4** and Bu$_3$SnH in benzene with visible light gave a mixture of **6a** and the S-pyridyl derivatives, **6c** and **7c**, while a similar experiment in the absence of Bu$_3$SnH afforded a mixture of **6c** and **7c** (3:1)[12] in 70% yield after chromatography. When **4** was generated *in situ* from the chloroformate of *trans*-hex-2-en-1-ol and the sodium salt of 2-mercaptopyridine-*N*-oxide in bromotrichloromethane, the product was a 2.2:1 mixture of the diastereoisomeric bromides, **6d** and **7d**, the structures of which were confirmed by independent synthesis.[13] The same bromides (**6d** and **7d**) were obtained in a ratio of 3.3:1 together with **6c** and **7c** when 2-bromo-2-chloro-1,1,1-trifluoroethane was employed as the bromine atom donor.[14] With diphenyl selenide, the carbonate **4**, when generated *in situ*, gave **6e** and **7e** in the ratio of 1.5:1. The yields of bromides and selenides from these experiments were modest (30-40%) due to extensive decomposition during the isolation procedure.



Scheme 1

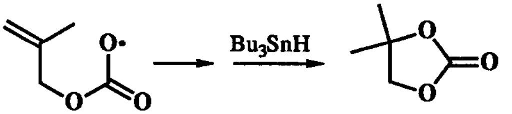
The results of each of the above experiments conform to expectation based on the mechanism of Scheme 1. Thus the radical **8**, generated by attack of a carbon (e.g. $\cdot CCl_3$), sulfur (e.g. $\cdot SBu^t$) or selenium (e.g. •SePh) centred radical on **4**, undergoes fast, exclusive *exo* cyclization to give the radical **9**. When no other chain carrier is present X-Y represents the precursor **4**, Y• = **9**, and diastereoselective S_H2 attack of **9** on **4** affords the products **6c** and **7c** and propagates the chain. ESR measurements[15] indicate that free rotation about the bond between the ring and the radical centre is very fast on the ESR time scale, and it appears, therefore, that the diastereoselectivity of the S_H2 step reflects the relative energies of the diastereoisomeric products, a conclusion supported by MM2 studies.

In reactions involving 2-bromo-2-chloro-1,1,1-trifluoroethane, S_H2 attack of the radical **9** on the precursor **4** competes with the desired transfer of Br•. Similarly, the reaction of **9** with Bu_3SnH competes with formation of **6c** and **7c**, while the formation of **9** by *exo* cyclization competes with H• transfer from Bu_3SnH to **8** to afford the carbonic acid **10**. Decarboxylation of the latter yields the alcohol **11**.

Steady state analysis of the reaction of **4** with Bu_3SnH (Scheme 1) shows that:

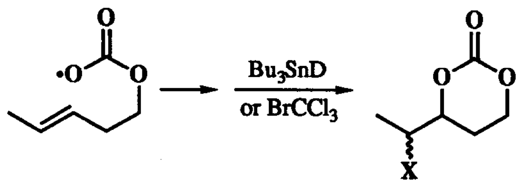
$$d[[\mathbf{6a}] + [\mathbf{6c}] + [\mathbf{7c}]]/d[\mathbf{11}] = k_c/k_H\,[Bu_3SnH].$$

Substitution into the integrated form of the results from careful analysis (^1H nmr) of the reaction mixtures conducted with various Bu_3SnH concentrations gave $k_c/k_H = 2.3$ M. No accurate figure for k_H is available but the suggested[16] minimum value of $2 \times 10^8\ M^{-1}s^{-1}$ implies that $k_c > 4.0 \times 10^8\ s^{-1}$ at 80°C.

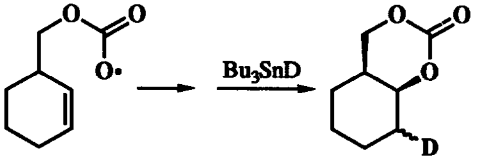


12 **13**

14 **15**



16 **17**, X = D
18, X = Br



19 **20**

In further experiments with appropriate precursors, the 5-substituted radical **12** was shown to undergo exclusive *exo* ring closure to give, ultimately, **13**, unlike its hex-5-enyl analogue which undergoes mainly *endo* cyclization.[17] The 4-substituted radical **14** underwent stereoselective *exo* ring closure in accord with established guidelines[18] to give mainly the *trans* product (*trans*-**15**/*cis*-**15** = 4:1).

Radicals containing a double bond correctly disposed for 1,6-ring closure underwent rapid *exo* cyclization. Thus the radical **16** when generated in the presence of Bu_3SnD gave the cyclic carbonate **17** as a mixture of diastereoisomers (1.2:1) in 45% yield. Similarly, the radical **19** underwent diastereoselective ring closure followed by diastereoselective D• transfer to afford a 3:1 mixture of the diastereoisomers **20** possessing a *cis* ring junction. The reaction of **16** with bromotrichloromethane gave a mixture of the diastereoisomers **18** in 33% yield.

Although the competing rearrangements of carbonate precursors, e.g. **4**, can be troublesome, we believe that the reactions above may have synthetic utility in the case of primary alkenyloxycarbonyloxy radicals. Unfortunately, the rearrangement becomes the dominant feature of carbonates derived from allylic secondary alcohols, and thus far has precluded their use as radical precursors.

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12. Assignment of the stereochemistry of the carbonates **6c** and **7c** was based on the similarity of their ^{1}H nmr spectra to those of the corresponding diastereoisomeric bromocarbonates **6d** and **7d**.
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