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CYCLIZATIONS AND INTERMOLECULAR ADDITIONS OF ALKOXYCARBONYLOXY RADICALS FROM *N*-HYDROXYPYRIDINE-2-THIONE CARBONATES

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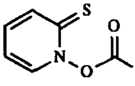
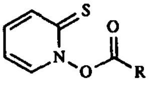
Abstract: Alkoxycarbonyloxy radicals from allyl and homoallyl alcohols cyclize in an *exo* fashion to give, respectively, 3-substituted 1,2-diol carbonates and 4-substituted 1,3-diol carbonates whereas simple alkoxycarbonyloxy radicals add intermolecularly to ethyl vinyl ether to give, ultimately, carbonates of glycolaldehyde derivatives.

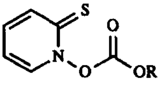
The application of radical methods in organic synthesis is becoming increasingly popular.[1] Heteroatom centered radicals are attractive in part due to the reversed polarity character of the radical. For example, aminium cation radicals from *N*-hydroxypyridine-2-thione carbamates (**1**) can cyclize onto unactivated olefin sites or add intermolecularly to electron rich olefins.[2] Carbamates **1** belong to a family of radical precursors, the progenitors of which are Barton's valuable PTOC esters (**2**),[3] that initially produce a variety of oxygen centered radicals by N-O bond cleavage. In this communication we report that alkoxycarbonyloxy radicals formed from another member of this family, *N*-hydroxypyridine-2-thione carbonates (**3**),[4] can be employed in synthetically useful conversions. Allyl- and homoallyloxycarbonyloxy radicals cyclize in a regiocontrolled *exo* fashion, and simple analogs add to electron rich olefins regioselectively. Depending on the subsequent trapping reaction, the overall sequence effects either an oxidation or hydrolysis of the alkene moiety.



1 (PTOC–NR_2)



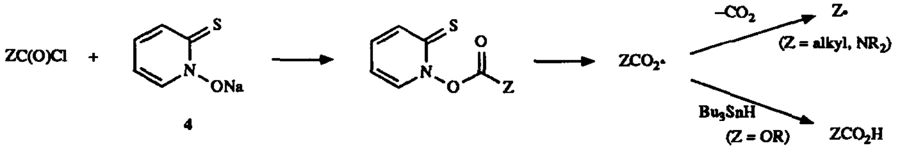
2 (PTOC–R)



3 (PTOC–OR)

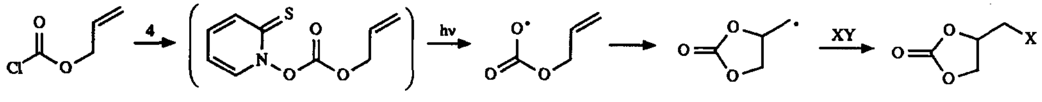
An example of a carbonate **3** was described by Beckwith and Hay who attempted to use it as a source of an alkoxy radical.[4] These radical precursors are prepared by reaction of the commercially available *N*-hydroxypyridine-2-thione sodium salt (**4**) with a chloroformate,[4] a general route that also can be used to prepare precursors **1** and **2**,[3,5] and they react in radical chain reactions in a manner similar to that of **1** and **2** (Scheme). Thus, a variety of radicals add to the thione moiety of **1**, **2** or **3** with subsequent or concomitant

Scheme



cleavage of the weak N-O bond to give carbamoyloxy, acyloxy or alkoxycarbonyloxy radicals, respectively. In the case of **1** or **2** (where R is alkyl), rapid decarboxylation follows because the radical thus formed is relatively stable. However, when the incipient radical is unstable (e.g. R in **2** is aryl, vinyl, etc.), the decarboxylation step is slow, and other reaction channels of the acyloxy radical emerge.[6] Similarly, decarboxylation of an alkoxycarbonyloxy radical to give an alkoxy radical is expected to be slow, and Beckwith and Hay found that Bu_3SnH trapping was faster than decarboxylation.[4] The potentially long lifetimes of alkoxycarbonyloxy radicals coupled with the general ease of preparation of the PTOC class of radical precursors and the facility with which their reactions can be controlled suggested that precursors **3** might be employed productively in synthesis.

Although several carbonates **3** can be produced by the reaction of a chloroformate with salt **4** as described,[4] we were unable to isolate precursor **5** from reactions of allyl chloroformate with salt **4** apparently due to the high polar reactivity of the allylic group (see below). Nevertheless, these reaction mixtures rapidly developed the faint yellow color characteristic of the PTOC class of intermediates suggesting that **5** was being formed.[7] When the isolation step was avoided and the reaction mixtures were simply irradiated with visible light within a few minutes of mixing,[8a] the cyclic carbonate **8**[9a,b,10] was produced in 85% isolated yield. A similar reaction performed in CH_2Cl_2 gave **8** in 66% yield. The radical chain reaction sequence involves production of the allyloxycarbonyloxy radical (**6**) that cyclized in a 5-*exo* fashion to give carbon radical **7** which subsequently attacked precursor **5** in a chain propagation step.

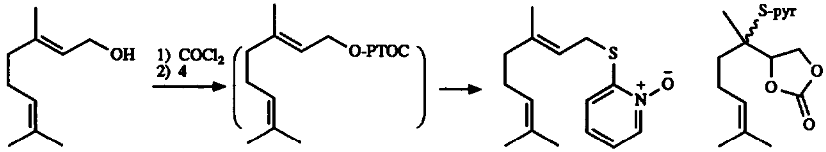


5 **6** **7**

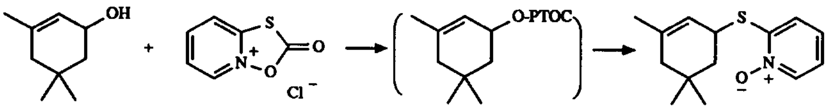
XY = **5** **8**; X = S-(2-pyr)
XY = Ph_2Se_2 **9**; X = SePh
XY = *t*-BuSH **10**; X = H
11; X = $CH_2CH(S\text{-}2\text{-}pyr)SO_2Ph$

Efficient trapping of the carbon radical **7** in competition with the self-trapping step was possible as expected.[3,11] For example, a mixture of allyl chloroformate, salt **4** and PhSeSePh was irradiated shortly after mixing[8b] to give in 70% isolated yield cyclic carbonate **9**[9a,b,10] which incorporates the readily functionalized phenylseleno group. Similarly, a mixture containing *t*-BuSH[8c] gave the cyclic carbonate of 1,2-propanediol (**10**)[9a,b,12] as the only product detected by NMR spectroscopy of the reaction mixture. In both of these cases, the S_H2 trapping reactions gave another radical (PhSe• and *t*-BuS•) that propagated the chain reaction by addition to PTOC carbonate **5**. When **5** was produced in the presence of phenyl vinyl sulfone,[8d] adduct **11**[9a,b,d,e] was obtained in 53% yield as a 1:1 mixture of diastereomers. In this reaction, radical **7** added to phenyl vinyl sulfone to give an adduct radical that then reacted with **5** in a propagation step.

Studies with geraniol and isophorol indicated the origin of the problem in attempted isolation of carbonate **5**. The reaction of geranyl chloroformate with salt **4** in a vessel shielded from light gave the adduct **12**[9a,b,d] in 76% yield. When the isolation step was avoided, radical derived products could be obtained in part; thus, a mixture of geranyl chloroformate and salt **4** was irradiated with visible light[8a] to give the thiopyridyl substituted cyclic carbonate **13** and adduct **12** in a 65:35 ratio; carbonate **13**[9a,b] was isolated in 50% yield as a 4:1 mixture of diastereomers. The reaction of isophorol with salt **14** and Et_3N in cyclohexane, another route



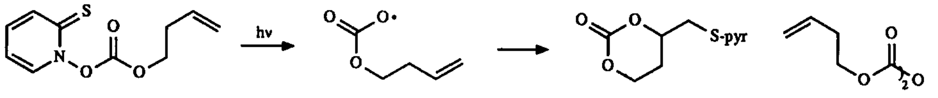
	12	13
dark	100	0
visible hν	35	65



14 15

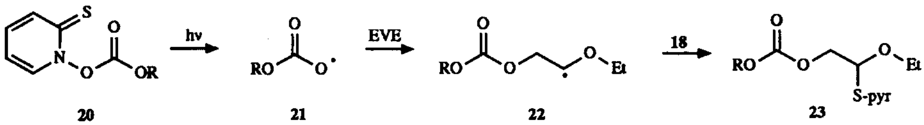
expected to yield the PTOC carbonate,[3] gave adduct **15**[9a,c,d] in 21% yield after chromatography. The formation of **12** and **15** in two distinct synthetic approaches suggests that the allylic PTOC carbonates were formed but rearranged (with loss of CO_2) via a concerted or dissociative intramolecular process.

The possibility of effecting a larger ring cyclization was studied with the 3-buten-1-ol system. In this case, the carbonate intermediate **16** was isolated from reactions of the corresponding chloroformate with salt **4**.[4] Visible light irradiation[13a] of the homoallyl PTOC carbonate **16**[7] gave the cyclic carbonate **18**[9a,b] and a by-product tentatively identified as the carbonate anhydride **19**[9a,b] in a 1:1 ratio. Based on Barton and Ramesh's observations with relatively stable acyloxy radicals,[6] the carbonate anhydride undoubtedly arose from self-trapping of the alkyloxycarbonyloxy radical **17** by the PTOC precursor followed by a complex series of polar reactions. The 6-*exo* radical cyclization of **17** is expected to be slower than the analogous 5-*exo* cyclizations based on known rates of carbon radical cyclizations.[14] When crude precursor **16** was added slowly to an irradiated reaction mixture to suppress the self-trapping reaction of **17** by dilution, cyclic carbonate **18** was obtained in 51% yield from 3-buten-1-ol.[13b]



16 17 18 19

Barton and Ramesh showed that the benzoyloxy radical added efficiently to ethyl vinyl ether in competition with reaction with its PTOC precursor,[6] and simple alkoxycarbonyloxy radicals would be expected to react similarly with electron rich olefins. When the simple carbonates **20**[7] were irradiated in solutions containing ethyl vinyl ether (EVE),[15] the glycolaldehyde derivatives **23** were formed. Product **23a**[9a,b,16] from the ethyl carbonate **20a** was obtained in 93% yield, and product **23b**[9a,b] was isolated in 81% yield from the three step sequence involving reaction of cyclopentanol with phosgene, reaction of the chloroformate with salt **4**, and visible light irradiation of carbonate **20b** in the presence of ethyl vinyl ether. Products **23c**[17] and **23d**[17] were obtained in crude yields of 65% and 40%, respectively, for the three step sequence from their corresponding alcohols, but these compounds decomposed on standing and attempted purification.



a: R = Et; **b**: R = *c*-C_5H_9; **c**: R = CH_2Ph; **d**: R = *t*-Bu

In summary, alkoxycarbonyloxy radicals from PTOC carbonates can be employed in both inter- and intramolecular reactions. The cyclizations of allyl- and homoallyloxycarbonyloxy radicals are potentially useful as radical-based alternatives for an overall oxidation or hydrolysis of a double bond. The *exo* mode of the radical cyclizations results in a regioselective addition of oxygen to the olefinic carbon nearer the original hydroxy group, and the cyclic transition state requires *syn* delivery of oxygen in the first step. The additions to electron rich olefins are expected to provide a variety of protected *vic*-diol or α-hydroxy carbonyl products. We are continuing to explore synthetic applications of alkoxycarbonyloxy radicals.

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2. See, for example, Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329. Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Ibid.* **1990**, *46*, 2345. Newcomb, M.; Kumar, M. U. *Tetrahedron Lett.* **1990**, *31*, 1675.
3. Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901.
4. Beckwith, A. L. J.; Hay, B. P. *J. Am. Chem. Soc.* **1988**, *110*, 4415. *Idem. Ibid.* **1989**, *111*, 240.
5. Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651.
6. Barton, D. H. R.; Ramesh, M. *Tetrahedron Lett.* **1990**, *31*, 949. Barton, D. H. R., private communication.
7. Precursor **5** could be detected and precursors **16** and **20** could be identified by ^1H NMR spectroscopy. However, in general, this group of compounds appears to aggregate in $CDCl_3$ solution; typically, the ^1H NMR spectrum contained broad peaks.
8. (a) Solvent benzene, room temperature, 0.1 M chloroformate, 0.1 M salt **4**, 5 min stirring then irradiation with a 150 W tungsten lamp at 0.3 m overnight, filtration of NaCl, solvent distillation, flash chromatography on silica gel with hexane-ethyl acetate (6:1) elution. (b) As above but at 0.05 M concentrations with 0.2 M Ph_2Se_2 present. (c) As above but at 0.05 M concentrations with 2 M *t*-BuSH present, no chromatography. (d) Solvent CH_2Cl_2, room temperature, 3 mmol of chloroformate added to an irradiated mixture containing 3.3 mmol of **4** and 15 mmol of phenyl vinyl sulfone over 1.2 h, chromatography on silica gel with ether-pentane and ether-ethyl acetate elution.
9. Characterized by (a) ^1H NMR spectroscopy, (b) ^{13}C NMR spectroscopy, (c) high resolution mass spectrometry, (d) IR spectroscopy, (e) elemental analysis.
10. The carbonate was further characterized by conversion to the dimethyl ether (hydrolysis with 0.5 M NaOH, treatment of the diol with NaH and MeI) which was characterized.[9a,b,c]
11. Newcomb, M.; Kaplan, J. *Tetrahedron Lett.* **1987**, *28*, 1615.
12. Product **10** was identical to an authentic sample prepared from 1,2-propandiol and phosgene.
13. (a) Conditions similar to those in note 8a, 0.05 M **16**. (b) 3-Buten-1-ol was added to 1 equiv of phosgene in toluene-ether. The solvent was distilled, and the crude chloroformate was allowed to react with 1 equiv of salt **4** in benzene. Following filtration of NaCl, the benzene solution containing crude **16** (ca. 0.05 M) was added in ten equal portions at 15 min intervals to an irradiated reaction vessel. The work-up was as in note 8a.
14. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4.
15. Conditions similar to those in note 8a, 0.05 M **20**, 1.75 M ethyl vinyl ether.
16. The product was further characterized by conversion to the 2,4-DNP derivative of glycolaldehyde ethyl carbonate.[9a,b]
17. Identified by ^1H NMR spectroscopy.
18. Related studies of alkoxycarbonyloxy radical cyclizations are reported in the accompanying communication.

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