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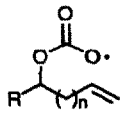
Diastereoselective 1,2- and 1,3-Diol Formation via Oxygen-Centered Radical Cyclizations

Martin Newcomb* and Bhavani Dhanabalasingam

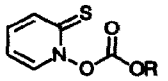
Department of Chemistry, Wayne State University, Detroit, MI, 48202-3489, USA

Abstract: Allylic and homoallylic alkoxycarbonyloxyl radicals, produced in chain reactions of 3-hydroxy-4-methylthiazole-2(3*H*)-thione carbonates, cyclize to give, ultimately, 1,2- and 1,3-diol carbonates in fair to good yield and, in some cases, high diastereoselectivity.

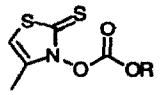
Radical based synthetic methods are increasing in popularity in part because they provide non-polar counterparts to conventional conversions.[1] A further impetus for considering a radical based synthetic approach is the growing understanding of and control of stereoselectivity in radical reactions.[2] Most of the efforts to develop radical methodology have focused on carbon-centered radicals reacting to form new C-C bonds. In this communication, we report a general protocol for construction of 1,2- and 1,3-diols via oxygen-centered radical cyclizations. These radical cyclizations are similar in their overall transformations to polar halogen induced cyclization reactions of carbonates and in some cases proceed with significantly higher diastereoselectivity than the polar analogs.



1: n = 0, 1



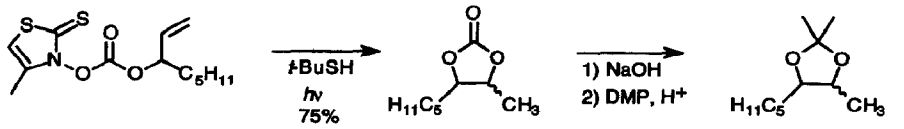
2, PTOC carbonate



3, TTOC carbonate

Applications of allylic and homoallylic alkoxycarbonyloxyl radicals (**1**) in diol producing reactions were explored by three groups.[3] All employed PTOC[4] carbonate radical precursors (**2**) that react in chain reactions to give radicals **1**. For allylic or homoallylic radicals **1** (R = H), highly regioselective cyclizations to 1,2- and 1,3-diol carbonates, respectively, occurred.[3] However, PTOC carbonates suffer two disadvantages that severely limit their potential utility. First, secondary allylic precursors **2** could not be produced; apparently, such intermediates decompose rapidly by an ionic pathway, and attempts to prepare them gave 2-(alkylthio)pyridine-*N*-oxides. Second, for the case of homoallylic alkoxycarbonyloxyl radicals **1** (n = 1), "self-trapping" by the PTOC precursor was fast relative to cyclization, and low yields of 1,3-diol carbonate products were obtained when reactions were not run at high dilution. We have found that both of these deleterious competing side-reactions are substantially suppressed by the use of a less reactive class of radical precursors, the TTOC (for thiazole-thione-oxy-carbonyl) carbonates **3**.[5]

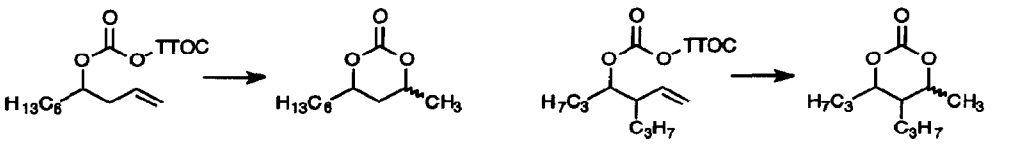
Radical precursors **3** were readily prepared by reaction of 3-hydroxy-4-methylthiazole-2(3*H*)-thione[5a] with the appropriate chloroformate. Isolation of precursors **3** is not necessary,[6] but those studied in this work were purified so that subsequent reactions could be characterized more completely. The stability of secondary allylic precursors **3** is noteworthy in light of the observations that primary allylic PTOC carbonates were unstable on standing and secondary allylic PTOC carbonates could not be produced.[3]



4 **5** **6**: *anti*:*syn* = 16

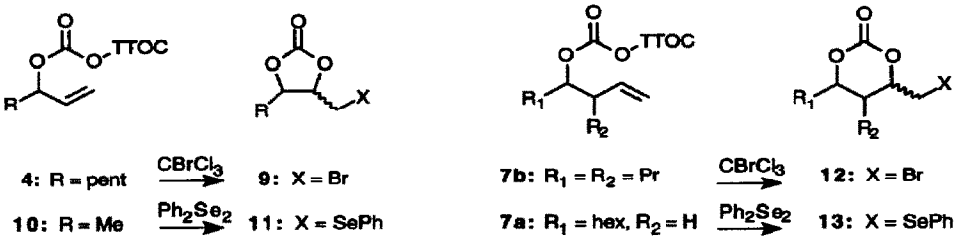
The efficacy of TTOC carbonates for production of 1,2-diols was apparent in the reactions of precursor **4**. A reaction conducted in the presence of *t*-BuSH gave a mixture of diastereomeric carbonates **5** in 75% isolated yield. Hydrolysis of the carbonates followed by conversion of the diols to their acetonides permitted a characterization of the products. The diastereomeric acetonides **6** were obtained in a 16:1 ratio, and the major diastereomer was identified as *anti* by comparison to an authentic sample produced by OsO_4 catalyzed dihydroxylation[7] of *trans*-2-octene followed by conversion of the diol to acetonide **6**.

A more severe test of the utility of TTOC carbonates was their application in 1,3-diol syntheses. The TTOC precursor **7a** reacted in the presence of *t*-BuSH to give carbonates **8a** in 57% isolated yield. Subsequent conversion of the carbonates to acetonides and ^{13}C NMR analysis[9] showed that the products were produced in a 4:1 *syn*:*anti* ratio. The pair of diastereomeric TTOC carbonate precursors[8] **7b** and **7c** reacted in the presence of the thiol to give carbonates **8b** (51% isolated, 66% based on recovered alcohol) and **8c** (50% isolated, 63% based on recovered alcohol). Conversion of **8b** and **8c** into acetonides permitted stereochemical identifications.[9] Diastereomers **8b** were obtained in a low ratio (3:1), whereas the diastereomeric ratio for **8c** was substantially higher (18:1).



7a **8a**: *syn*:*anti* = 4 **7b**: 1,2-*syn* **7c**: 1,2-*anti* **8b**: 1,3-*anti*:1,3-*syn* = 3 **8c**: 1,3-*syn*:1,3-*anti* = 18

As with other members of the broad family of radical precursors based on thiohydroxamic acids,[4] oxidative trapping following the radical cyclization reactions was possible. For example, when **4** was allowed to react in the presence of $CBrCl_3$, the bromine substituted carbonates **9** were obtained in 70% isolated yield, and reaction of TTOC **10** in the presence of PhSeSePh gave the phenylselenyl substituted carbonates **11** in 55% isolated yield. In a similar manner, TTOC **7b** gave bromocarbonates **12** in 61% isolated yield (84% based on recovered alcohol), and TTOC **7a** gave phenylselenyl substituted carbonates **13** in 56% isolated yield (81% based on recovered alcohol).



When oxidative radical trapping with $CBrCl_3$ is employed in the final step of the chain reaction sequence, the products (e.g. **9**, **12**) are closely related to those obtained in halogen induced cyclizations of allylic and homoallylic carbonates,[10] and, in fact, the bromocarbonates can be converted to epoxide alcohols in much the same manner as the related iodocarbonates.[11] A comparison of the diastereoselectivity of the two approaches to diols is useful. For each case in which a comparison can be made, the radical and polar reactions gave the same major diastereomer. The diastereoselectivity in the radical cyclization producing the 1,2-diol (precursor **4**, 16:1) is much greater than that observed in polar cyclizations of analogous allylic carbonates[10a] (ca. 4:1). For the 1,3-diol syntheses, the radical cyclization with no substituent at C-2 (**7a**) gave low selectivity (4:1) in comparison to analogous polar reactions[10] (as high as 25:1). However, for the case with reinforcing alkyl groups at C-1 and C-2 (**7c**), the energy difference in the diastereomeric transition states for the radical reaction was much greater than that for the polar case; **7c** gave an 18:1 ratio of products at 20 °C, whereas the selectivity in corresponding polar carbonate cyclizations[10c] was optimized to 14:1 at –95 °C.

Although TTOC precursors **3** obviously did not trap radicals **1** as rapidly as did the PTOC precursors **2**, we believe that TTOC "self-trapping" reactions still compete in the case of homoallylic radicals **1** (n = 1). Specifically, we consistently isolated low yields of unreacted alcohols from reactions of purified precursors **7**. It is most likely that the alcohols were regenerated by hydrolysis of carbonate anhydrides during the chromatographic purifications; carbonate anhydrides are the expected ultimate products from self-trapping of the oxyl radicals **1**.[3a,12] Alcohols were recovered when the oxidative trapping agents ($CBrCl_3$ and PhSeSePh) were employed as well as when *t*-BuSH was present, and, therefore, it is unlikely that the polarity mis-matched thiol trapped radicals **1** in competition with the cyclizations. If TTOC self-trapping is the major side reaction, then, for recalcitrant systems, yields might be improved by dilution of the reaction mixtures.

The TTOC carbonates are readily prepared from alcohols via the chloroformates and can be handled with no special precautions. Highly regioselective *exo* cyclizations of allylic and homoallylic alkoxycarbonyloxyl radicals giving 1,2- and 1,3-diols, respectively, were already known from studies with PTOC carbonate precursors **2**,[3] and we found no evidence for *endo* cyclizations in this work. The good diastereoselectivity observed in the reactions of **4** and **7c** in comparison to that obtained in analogous polar cyclizations of carbonates suggests that the radical-based diol synthesis can compliment the polar method.

General procedure for preparation of TTOC carbonates. To a cold (0 °C) solution of phosgene (23 mmol) in 12 mL of toluene was added 4 mmol of alcohol and 4.3 mmol of Et_3N in 2 mL of benzene. After 2 hours at 0 °C, excess phosgene and solvents were removed at reduced pressure. The crude chloroformate was dissolved in 30 mL of benzene, and to this solution was added a mixture of 3-hydroxy-4-methylthiazole-2(3*H*)-thione[5a] (4 mmol) and Et_3N (4.3 mmol) in 5 mL of benzene. After 3 hours at 20 °C, the solvent was removed at reduced pressure, and the crude TTOC carbonate was purified by chromatography on silica gel (EtOAc--hexanes; 15:85 v:v). The TTOC carbonates

were isolated in 60-65% yield. The crude TTOC carbonates could be employed in subsequent reactions without purification.[6]

General procedure for reactions of TTOC carbonates. The TTOC carbonate (ca. 0.7 mmol) was dissolved in 13 mL of benzene in a quartz tube, and the desired trapping agent was added. Final concentrations of trapping agents were ca. 0.2 M (*t*-BuSH and $CBrCl_3$) or 0.15 M (PhSeSePh). The tube was sealed with a rubber septum, purged with Ar, and photolyzed in a photochemical reactor (70 W, 300 nm bulbs) for 3 hours. Solvent was removed, and the carbonate products were purified by chromatography on silica gel (EtOAc--hexanes; 20:80, v:v).

For **stereochemical assignments** of 1,3-diol products, the crude carbonate products from reactions conducted in the presence of *t*-BuSH were hydrolyzed (50% solution of NaOH in dioxane, 1 hour),[13a] and the crude diols obtained were converted to their acetonides (PPTS catalyzed reaction with 2,2-dimethoxypropane in acetone).[13b] The product ratios of the acetonides were determined by GC, and the identities were determined by ^{13}C NMR spectroscopy.[9]

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