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Reactions of α,α′-Dihydroxy Ketones with Phosgene. Structural Requirements for Spiro Epoxy Carbonate Formation

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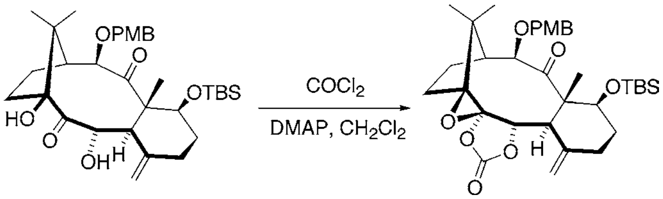
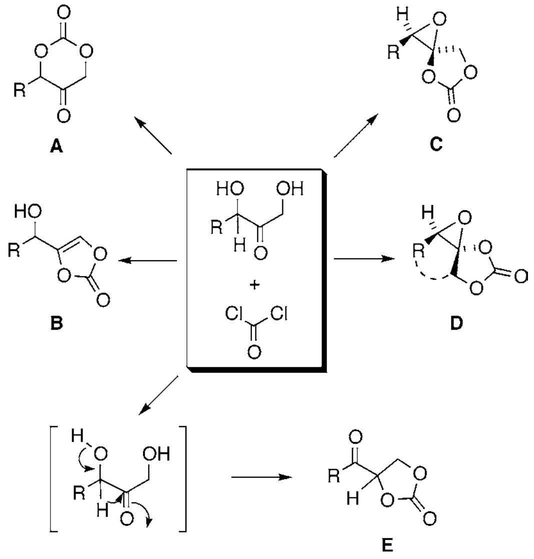
ABSTRACT



α,α′-Dihydroxy ketones having two OH groups that can come into close proximity react with phosgene in the presence of DMAP to produce 1,3-dioxane-2,5-diones. When covalent bonding in this manner is prohibited, alternate reaction pathways can in principle be adopted. Of these, the generation of spiro epoxy carbonates is shown to be feasible in three examples. In other cases, the α-ketol rearrangement precedes diacylation.

The reaction of phosgene with α,α′-dihydroxy ketones constitutes a process that has to our knowledge not been previously explored. In conjunction with a total synthesis project, such a chemical transformation loomed as potentially desirable for a specific application. On closer consideration of the mechanistic options available to this reagent combination, however, a myriad of product alternatives suggested themselves (Scheme 1). The simplest and most direct inference to be drawn is that diacylation will materialize to generate 1,3-dioxane-2,5-diones **A**. Seemingly, provision need also be made under the proper circumstances for possible regiocontrolled enolization of the substrate with formation of a vinylene carbonate of type **B** or regioisomers thereof. Adding to the potential intricacies awaiting the application of this chemistry is capture of the oxirane tautomer of the reactant. One or both of the two isomeric epoxy carbonates **C** and **D** would result, with the conversion being restricted to **D** if a small ring were present as implied by the dashed loop. To our knowledge, the functionality resident in **C** and **D** has not yet been recorded in the chemical literature.

Scheme 1. Possible Reaction Pathways



Yet another option would entail a preliminary α-ketol rearrangement in advance of phosgene capture as in **E**. The illustrated example entails a hydrogen shift, but 1,2-alkyl migration is also intrinsically possible. The inherent challenge

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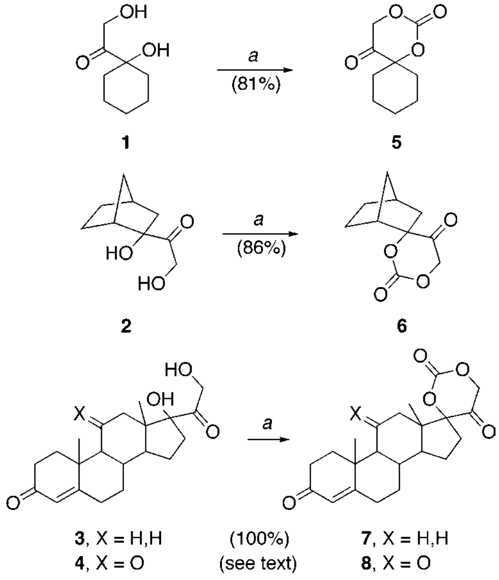
of clarifying these issues while simultaneously factoring in stereochemical interdependencies where relevant compelled us to conduct a number of probe experiments as described herein.

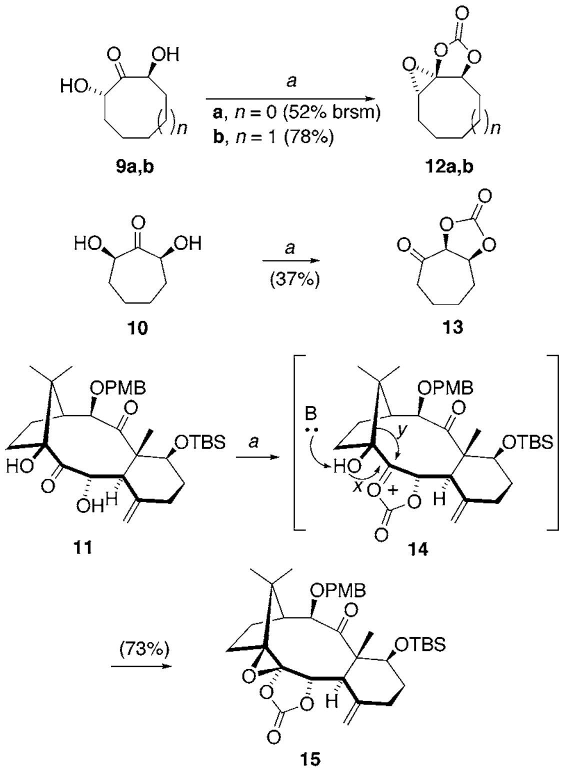
Initial attention was accorded to **1**−**4**, α,α′-dihydroxy ketones featuring all oxygenated functionality exocyclic to a ring system (Scheme 2). The first two candidates were prepared by the 1,2-addition of 2-lithio-1,4-dioxene to cyclohexanone and 2-norbornanone, respectively, followed by peracid oxidation, borohydride reduction, and acidic hydrolysis.[2,3] Steroids **3** and **4** were kindly provided by Prof. Angelo Liguori.[4] Identical reaction conditions were applied throughout. Although the reagents were admixed at −78 °C, little product formation was observed until the reaction mixtures reached approximately 0 °C. In all four examples, thin-layer chromatographic analysis indicated a single product to result. As a consequence of the sensitivity of these compounds to silica gel chromatography, a careful workup protocol was mandated. The procedure of choice involved initial dilution with saturated $NaHCO_3$ solution followed by washing of the separated organic layer with half-saturated $CuSO_4$ solution to remove the DMAP. After drying, solvent evaporation led to pure crystalline products. We note here that the tetracarbonyl derivative **8** proved to be highly sensitive, with >90% reversal to **4** occurring under the predescribed conditions. Pure **8** was ultimately secured by filtration through a plug of silica gel that had been pretreated with triethylamine.

Scheme 2. Dioxanedione Formation



On the basis of the above precedents, it would seem reasonable to assume that α,α′-dihydroxy ketones that have significant levels of conformational freedom available to them will react with phosgene in the manner shown in Scheme 2. To bring about the operation of an alternative pathway, we turned to structurally more restricted examples. The stereoisomeric pairs **9** and **10**[5] came to be regarded as serviceable candidates (Scheme 3). For the cis hydroxyl arrangement in **10** to be conducive to cyclic carbonate formation, bicyclic features would necessarily materialize, thereby ushering in ring strain. The trans arrangement in **9** is incompatible with this particular reaction pathway, since formation of an inside/outside bicyclic will certainly be skirted.

Scheme 3. Fate of Conformationally Restricted Systems



In fact, cycloheptanone **9a** proved to be an early harbinger of an altered reactivity profile since only 20% consumption was seen after 2 days at room temperature. For **1**−**4**, wholesale conversion to product occurred after only 1−2 h. Moreover, epoxy carbonate **12** was generated exclusively. Proof of the structural assignment to **12a** was amply furnished by comparative analysis of its infrared carbonyl stretching frequency and ^{13}C NMR chemical shifts (Table 1). It will be recognized that the additional CH_2 group in **9b** results in increased flexibility within the polymethylene chain. As minimal as this effect may appear to be, the efficiency with which **12b** is formed increases to the unoptimized level of 78% after 24 h. The spectral properties of this lone product were equally consonant with the presence of two strained rings.

The constraints resident in **10** are such that conversion to keto carbonate **13** operates. A preliminary α-ketol rearrangement serves to position the two hydroxyls in a cis, vicinal

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(1) Paquette, L. A.; Hofferberth, J. E. *Org. React.* **2003**, *62*, 477.

(2) Fetizon, M.; Goulaouic, P.; Hanna, I. *Tetrahedron Lett.* **1985**, *26*, 4925.

(3) These syntheses were carried out by Mr. James Eppich.

(4) Di Goia, M. L.; Leggio, A.; Le Pera, A.; Liguori, A.; Napoli, A.; Siciliano, C.; Sindona, G. *Tetrahedron Lett.* **2001**, *42*, 7413.

Table 1. Spectral Parameters of the Carbonate Products

compd	IR (cm^{-1}, film)	^{13}C NMR (δ, C_6D_6 or $CDCl_3$)
A. 1,3-dioxane-2,5-diones		
5[a]	1778, 1746	148.2, 203.0
6[a]	1766, 1743	149.4, 202.5
7[a]	1770, 1738, 1668	148.2, 196.8, 201.5
8[a]	1770, 1739, 1711, 1668	148.2, 197.3, 20 0.8, 205.8
B. keto carbonate		
13[b]	1815, 1738	153.6, 203.6
C. spiroepoxy carbonates		
12a[b]	1820	106.0, 152.4[c]
12b[b]	1819	107.9, 151.0[c]
15[a]	1828	111.6, 151.5, 218.1[c]

[a] C_6D_6 solution. [b] $CDCl_3$ solution. [c] Resonances that appear between 106 and 112 ppm are attributed to the dioxygenated spirocarbons.

relationship notably conducive to diacylation. Product **13** was independently synthesized by condensing *cis*-2,3-dihydroxy cycloheptanone[5] with phosgene.

The analogous treatment of **11**[6] proceeded with rapid conversion to **15** (1 h, 73%). As a result of the high crystallinity of this spiropentacyclic ketone, its detailed structural composition could be secured by single-crystal X-ray diffraction methods. The relevant ORTEP diagram (Figure 1) corroborates the exclusive operation of pathway x in **14**. Thus, deprotonation of the bridgehead hydroxyl group initiates nucleophilic attack by oxygen on the proximal phosgene-activated carbonyl functionality. No evidence was found for possible operation of a competitive 1,2-alkyl shift (e.g., pathway y) despite the fact that stereoalignment issues (including the alternative migration involving the ethano bridge) are not unreasonable expectations in this example.[6]

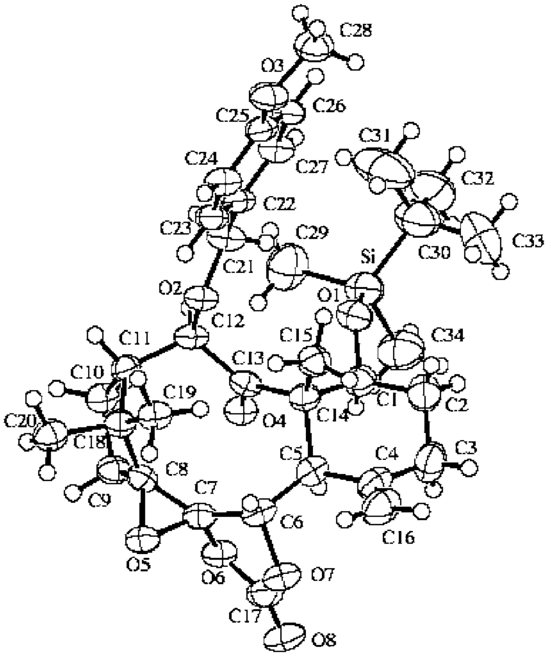

Figure 1. Molecular structure of **15** depicted with 50% probability displacement ellipsoids for the non-hydrogen atoms.

Another feasible pathway that links **11** to **15** can be envisioned wherein the order of nucleophilic attack by hydroxyl and acylation on the erstwhile ketone oxygen via a chlorocarbonate is reversed. While this fine distinction cannot be made unequivocally, we consider it quite likely that the *O*-acyl oxacarbenium intermediate drawn specifically for **14** may be a common intermediate to the entire structural ensemble examined in this study. Thus, 1,3-dioxane-2,5-dione formation would come about by attack of the hydroxyl group on the carbonyl carbon when structurally or conformationally permitted in flexible cases. The same intermediate would be very prone to enolization (in cases with enolizable protons), thereby leading to the observed (and known) carbonyl transposition, and it can definitely lead to spiro epoxides via pathway x.

In summary, we have demonstrated that α,α′-dihydroxy ketones whose OH groups cannot attain a reasonable level of proximity sufficient to react directly with phosgene nevertheless engage in alternative covalent bonding to this reagent. Proper reactant assembly can give rise to other structural arrays of interest. Presently, examples of spiro epoxy and keto carbonate generation are given. In contemplating possible extensions of this overall condensation process, specific attention needs to be given to the particular structural ensemble to be investigated.

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Supporting Information Available: Experimental details and spectroscopic properties of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Vilotijevic, I.; Yang, J. *J. Org. Chem.* Submitted.

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