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Ring Opening of 1,5-Dioxaspiro[3.2]hexanes: Selective Preparation of α-Heterofunctionalized-β′-hydroxy Ketones or 2,2-Disubstituted Oxetanes

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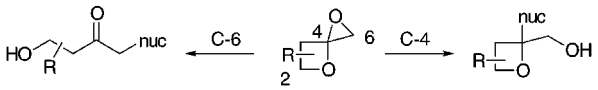
ABSTRACT



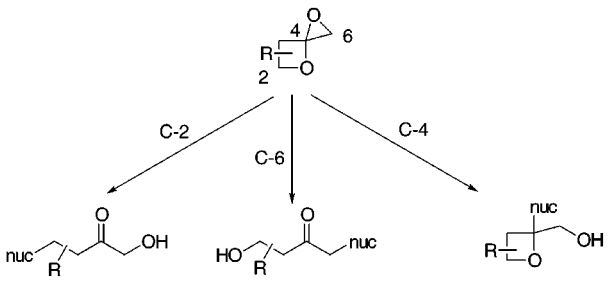
2-Methyleneoxetanes have been converted into 1,5-dioxaspiro[3.2]hexanes with dimethyldioxirane. Reaction of the dioxaspirohexanes with a range of heteroatom nucleophiles, hydride donors, or organoaluminum reagents was successful under neutral or mild conditions, affording, selectively, polyfunctionalized ketones or 2,2-disubstituted oxetanes.

We have recently developed the first general synthesis of 2-methyleneoxetanes[1] and have begun to investigate the reactivity of this fascinating class. We anticipated that the electron-rich enol ethers should undergo facile epoxidation to give 1,5-dioxaspiro[3.2]hexanes, a reaction that had precedent in the oxidation of allenes to allene oxides and 1,4-dioxaspiro[2.2]pentanes developed by Crandall and coworkers.[2] Indeed, after some experimentation we found that treatment of 2-methyleneoxetanes with anhydrous dimethyldioxirane (DMDO)[3] produced the corresponding dioxaspirohexanes in excellent yield.[4] Although we appreciated the unusual structure of this class of compounds (a search of the literature revealed no general preparation and only two previous examples of 1,5-dioxaspiro[3.2]hexanes as unexpected outcomes of unrelated experiments),[5] we were more interested in exploiting their presumed lability.

Our initial goal was to investigate the reactivity of 1,5-dioxaspiro[3.2]hexanes, particularly to ring-opening reactions. In principle, attack by nucleophiles could occur at C-2 or C-6 (Scheme 1), as either would release the considerable strain energy in these molecules, and ring openings of both oxetanes and oxiranes are known.[6] We might anticipate, however, that attack at C-6 would be preferred due to the greater reactivity of oxiranes. A third possibility (Scheme 1), reaction at C-4 resulting in ring opening of the oxirane alone, was deemed less likely but could not be discounted.

In general, ring-opening reactions of epoxides require the use of highly reactive organometallic reagents or the as-

Scheme 1



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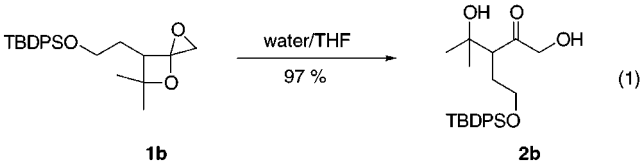
sistance of Lewis acids to be effective. Two factors, however, can make oxirane ring opening much less demanding. The presence of a heteroatom on the epoxide greatly enhances its susceptibility to cleavage, and this has been used as a valuable approach to α-functionalized carbonyl compounds.[7] In other cases, the release of strain energy associated with opening some simple or polycyclic epoxides makes them undergo ring opening or rearrangement reactions under mild conditions.[8] Dioxaspiro[3.2]hexanes contain both of these reactivity-enhancing elements, and we expected them to be sensitive to neutral C−O bond cleavage. This expectation appeared justified when treatment of **1b** with water in the absence of any acid or base gave the ring-opened dihydroxy ketone **2b** in nearly quantitative yield (eq 1). This prompted us to investigate a number of other nucleophiles in this reaction, and herein, we report our results.

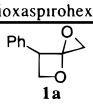
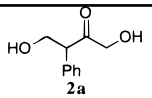
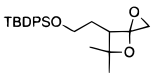
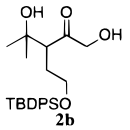
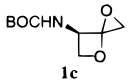
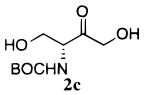
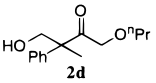
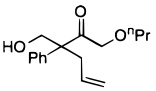
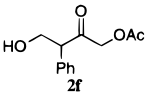
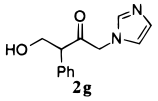
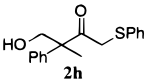
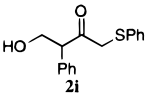
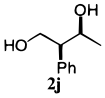
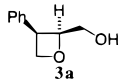
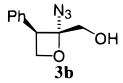
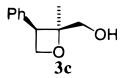


1b **2b** (1)

Oxygen-centered nucleophiles such as water and alcohols are effective without added base (Table 1). A TBDPS ether (**2b**) and a carbamate (**2c**), as expected, survive these mild conditions. The hydrolysis of 1,5-dioxaspiro[3.2]hexanes proceeded somewhat more slowly than the corresponding reactions of 1,4-dioxaspiro[2.2]pentanes as performed by Crandall and co-workers[2] (2 d vs 2 h), and a similar time differential was noted on reaction with propanol. However, in the latter case potassium carbonate or sodium hydride was used by Crandall to accelerate the alcoholysis. Other differences in the reactivity of these two systems were noted. Thus, thiophenol alone is effective in ring cleavage of 1,4-dioxaspiro[2.2]pentanes (21 h, 55%)[2] but not 1,5-dioxaspiro-[3.2]hexanes (**2h**, 7 d, 30%). However, the thiophenoxide anion is, not surprisingly, much more effective (**2i**, 2h**,** 70%). Among other nucleophiles, acetate works well (**2f**) but not imidazole (**2g**). So far, we have not been able to efficiently promote ring opening of dioxaspirohexanes with amines. Although there are many methods for the preparation of α-functionalized ketones,[9] they frequently encounter regioselectivity problems, require organometallic reagents at low temperature, or are limited to a single class of α heteroatom. Consequently, this method appears to be competitively versatile.

When we switched to nucleophiles that were not used in Crandalls work, we observed some unexpected and interesting results. Thus, lithium aluminum hydride proceeded as above, giving the 1,3-diol (**2j**) as a 15:1 mixture of

Table 1

Dioxaspirohexane	Nucleophile	Product	Yield (%)
 **1a**	water	 **2a**	61
 **1b**	water	 **2b**	97
 **1c**	water	 **2c**	83
 **1d**	n-propanol	 **2d**	87
 **1e**	n-propanol	 **2e**	70
1a	Bu_4NOAc	 **2f**	81
1a	imidazole	 **2g**	23
1d	PhSH	 **2h**	30
1a	PhSNa	 **2i**	70
1a	$LiAlH_4$	 **2j**	93[a]
1a	DIBAL	 **3a**	68
1a	$TMSN_3$	 **3b**	56
1a	Me_3Al	 **3c**	79

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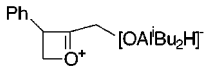
diastereoisomers, resulting presumably from initial reductive ring opening of the dioxaspirohexane at C-6 and reduction of the resulting intermediate β-hydroxy ketone. DIBAL, however, gave a different result. There a dramatic reversal in regioselectivity was observed arising from ring opening at the least expected position, C-4, to give the oxetane **3a**. The formation of **3a** can be rationalized by coordination of the Lewis acid to the epoxide oxygen with possible participation of the oxonium ion **4**. Other Lewis acid-linked



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nucleophiles produced identical results. Thus, $TMSN_3$ or Me_3Al gave the corresponding 2,2-functionalized oxetanes **3b** or **3c**. Evidence for oxonium ion **4**, or a related species, as a reactive intermediate comes from the diastereomeric ratio of the products **3a**−**c**. The dioxaspirohexanes **1a**−**e** were prepared according to our published procedure[4] and were isolated as diastereomeric mixtures (**1a** 14:1, **1b** 1.1:1, **1c** 6:1, **1d** 6:1, **1e** 3:1). It is noteworthy that for the reactions described in the previous paragraph the spiroketal asymmetric center was destroyed. Thus, the diastereomeric purity of the reactants was inconsequential. However, in the reaction of DIBAL with **1a** (a 14:1 mixture of diastereoisomers), **3a**, as an 8:1 mixture, was produced. Further, **3b** and **3c**, also prepared from **1a**, were isolated as single diastereoisomers. In **3a** and **3c** the relative stereochemistry, a trans relationship between the incoming nucleophile and the phenyl group, was determined by NOE experiments. The structure of **3b** was assigned by analogy with these two results.

In summary, we have demonstrated that 1,5-dioxaspirohexanes are cleaved regioselectively to give polyheterofunctionalized compounds, suitable for further elaboration. Our preliminary results indicate that the regioselectivity of ring opening is controlled by the nature of the nucleophile and the conditions used. Studies on the ring opening of 1,5-dioxaspiro[3.2]hexanes with other nucleophiles and the application of these observations to the synthesis of cyclic and acyclic natural products are the focus of ongoing studies.

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Supporting Information Available: Experimental procedures and characterization data, as well as high-resolution ^1H NMR spectra for those new compounds for which elemental analyses are not reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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