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Synthesis of Medium Size Rings Containing Oxygen and Sulfur by Ring Expansion of Halodioxolanes, Dioxanes and Oxathiolanes

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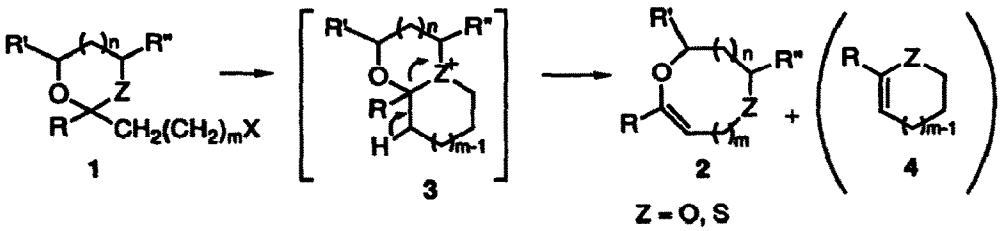
Abstract : Ring expansion of the readily available cyclic haloketals and halo-O,S-ketals provides a versatile method for the synthesis of medium rings containing sulfur and/or oxygen atoms.

Medium rings are generally difficult to synthesize via standard cyclization methodologies.[1] A well-recognized strategy for the construction of medium size rings is fragmentation of a bicyclic system composed of smaller, more easily synthesized rings.[2,3] Recently, we reported that halo cyclic thioketals serve as useful starting materials for the construction of medium size, sulfur containing ring systems via a cyclization/fragmentation mechanism.[4] As an extension of this methodology we wish to report the analogous ring expansion of halo-O,S-ketals and ketals.

An investigation of the ring expansion reactions of O,S-ketals (1, Z = S) was conducted in the hope that medium sized ethers could be synthesized through a sulfur extrusion reaction of the ring expansion products. Such ethers are commonly found in marine natural products.[5] As expected, in all cases the ring expansion products (2) arising from chemoselective alkylation of the sulfur atom were obtained in good yield.[6] A variety of substituents are tolerated in the starting material (Table 1, Entries 1-3) and may be used to produce functionalized medium sized rings. Studies on the sulfur extrusion reactions required to produce ethers from 2 are in progress.



Scheme 1

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Surprisingly, we also found that dioxanes and dioxolanes (1, Z = O) undergo analogous ring expansion reactions (Scheme 1). Although the conditions necessary for the oxygen ring expansion are harsher than those employed for the reaction of the thioketals, it is still a general reaction as shown in Table 1 (Entries 4-10). Thus, refluxing the haloketals (1, Z = O) overnight in DMF in the presence of diisopropylethylamine leads, in fair to good yield, to the dioxacycloalkenes (2, Z = O). For the chloroketals (1, Z = O, X = Cl) it was necessary to add potassium iodide as a catalyst.

Table 1. Ring Expansion of Various Halo Oxathiolanes, Dioxolanes and Dioxanes.

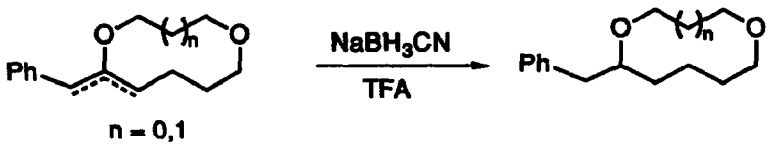
Entry[a]	Cmpd	R	n	m	X	Z	Ring Size	Product	Yield[b] (%)
1	**1a**	Ph	0	2	Cl	S	8	Z-2a	82
2[c]	**1b**	Ph	0	2	Cl	S	8	Z-2b	80
3[d]	**1c**	Ph	0	2	Cl	S	8	Z-2c	78
4	**1d**	*p*-FPh	0	2	Cl	O	8	Z-2d	86
5	**1e**	Ph	0	2	Cl	O	8	Z-2e	55[e]
6	**1f**	Ph	0	3	Br	O	9	Z-2f	24[f]
7	**1g**	Ph	1	3	Cl	O	10	Z-2g	60[e]
8	**1h**	Ph	1	2	Cl	O	9	Z-2h	50
9	**1i**	$PhCH_2$	0	3	Cl	O	9	Z- & exo 2i	37[f,g]
10	**1j**	$PhCH_2$	1	3	Cl	O	10	Z- & exo 2j	38[f,h]

[a]For entry 1 and 4-10 R' = R" = H. [b]Isolated yield. [c]R' = H; R" = Ph. [d]R' = *t*-Butyldimethylsiloxymethyl; R" = H. [e]Hydrolysis of the ring expansion products was observed in ~20% yield. [f]Elimination of hydrogen halide and the ring fragmentation products (4) were observed [g]Reduced to the dioxacyclononane in 10% overall yield from 1i. [h]Isolated yield of reduced dioxacyclodecane.

We believe that the mechanism of this reaction is analogous to that of the sulfur ring expansion.[4] Thus, intramolecular alkylation of one of the oxygen atoms by the primary halide yields an oxonium intermediate (Scheme 1, 3) which fragments to the dioxacycloalkenes (Scheme 1) with overall loss of the hydrogen halide. As was the case in the sulfur ring expansion we also occasionally isolated the ring fragmentation products (4). These may arise from an alternative breakdown of the oxonium intermediate 3, and so lend support to our postulated mechanism.

When the ketal is formed from an alkyl ketone (e.g. 1i, j) both *endo* and *exo* double bond isomers result. In order to simplify the analysis of these reactions, the crude ring expansion products were reduced to the corresponding saturated cyclic ethers. Conventional reagents such as H_2/Pd and triethylsilane/trifluoroacetic acid failed to give the desired products. However, reaction with sodium cyanoborohydride/ trifluoroacetic acid in

THF gave the desired ethers in fair to good yield (Scheme 2). This (unoptimized) reaction extends the scope of the ring expansion protocol to include the production of saturated heterocycles, and its utility in organic synthesis is currently being investigated.



Scheme 2

Interestingly, in entry 7 in Table 1 only the Z-isomer of the product was observed. In contrast, the ring expansion of the corresponding halo-thioketal gave the E-isomer as the major product.[4] This dichotomy may simply be a reflection of the greater strain in the *trans* isomer of a ten membered cycloalkene that contains four C-O bonds rather than four longer C-S bonds.

Table 1 also indicates that the expansion of a dioxolane with a four carbon side chain gives a poorer yield (entries 6 and 9) than all other combinations. Consistently more elimination of the halide to give the corresponding terminal alkene is also seen in these reactions. This partitioning into other pathways is perhaps due to two unfavorable effects that occur in this type of ketal. First, the intermediate oxonium ion requires the formation of a six membered ring which would occur more slowly than the corresponding five membered ring. Secondly, the lone pairs on the oxygens of a dioxolane may have less *p* character, and so be less nucleophilic, than those of a dioxane because of changes in orbital mixing to accommodate the different ring angles. Such an explanation has been suggested to account for the differences in complex formation of tetrahydrofuran and tetrahydropyran with dimethylzinc.[7] The dioxolane/C_4 sidechain system is the only one in which both effects occur, allowing other pathways such as elimination to compete with ring expansion.

In summary, we have introduced novel methodology for the conversion of oxathioketals and ketals into medium sized heterocycles containing two heteroatoms. The reaction occurs in fair to good yields under relatively mild conditions. The scope and utility of this reaction, as well as the synthetic transformations of the produced heterocycles, are currently being investigated.

General Procedure for Oxygen Ring Expansion. Diisopropylethylamine (5 mmol) was added to a solution of the haloketal (1 mmol) in dry DMF (5 ml) and the solution stirred under reflux for 16 h. (For chloroketals, catalytic potassium iodide (1 mmol) was added to the reaction.) After cooling, water and ether were added. The organic phase was separated, washed with brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by flash column chromatography (silica gel, typical eluent: hexane:ethyl acetate = 9:1). All products had physical data (NMR (^1H and ^{13}C), MS/HRMS and/or elemental analysis) consistent with the assigned structures.

Reduction of the Cyclodioxoalkenes. To a THF solution (10 ml) of the crude ring expansion product (from 1 mmol of the corresponding haloketal) and sodium cyanoborohydride (5 mmol), trifluoroacetic acid (10

mmol) was added slowly at 0°C. The mixture was stirred at room temperature overnight and diluted with ether, washed with sodium bicarbonate and brine, and dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography.

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