Letter

Preparation and reactions of 4-oxaspiro[2.3]hexanes†

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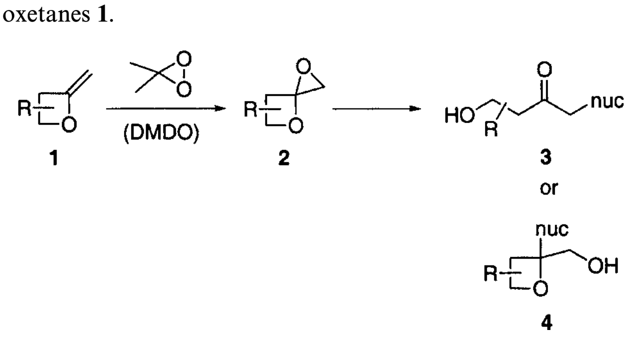
2-Methyleneoxetanes were converted in excellent yields to 4-oxaspiro[2.3]hexanes under modified Simmons–Smith conditions. Treatment of the oxaspirohexanes with $BF_3 \cdot Et_2O$ provided cyclopentanones, cyclobutanones or 4-methylene-tetrahydrofurans, depending on the substituents.

We have recently developed the first general synthesis of 2-methyleneoxetanes **1**[1] and have found this class of strained heterocycles to display a diverse range of reactivities. We anticipated that the electron-rich exocyclic enol ethers of **1** would provide a useful handle for reactions with electrophiles. Indeed, 2-methyleneoxetanes were shown to undergo facile and efficient epoxidation with anhydrous dimethyldioxirane (DMDO) to give 1,5-dioxaspiro[3.2]hexanes **2**.[2] Moreover, **2** displayed a fascinating dichotomy in reactions with nucleophiles, yielding multifunctionalized ketones **3** with most neutral and anionic nucleophiles but resulting in 2,2-disubstituted oxetanes **4** in the presence of some Lewis acids (Scheme 1).[3] Another class of compounds that we anticipated would be accessible and of interesting reactivity was the 4-oxaspiro[2.3]hexanes **5**. In this communication, we report their preparation and describe our initial observations on their reactivity.

Previous preparations of compounds containing the 4-oxaspiro[2.3]hexane framework are limited.[4–9] The one example directly related to our work involved the conversion of β-tosyloxyketone **6** to the α-alkylidene oxetane **7**.[7] Reaction of **7** with dichlorocarbene afforded 4-oxaspiro[2.3]hexane **8**. Direct insertion of a methylene group would be more broadly useful and was, consequently, our goal in investigating the preparation of 4-oxaspiro[2.3]hexanes **5** from 2-methyleneoxetanes **1**.



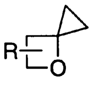
Scheme 1

2-Methyleneoxetanes **1a**–**1c**[1] and **1e**[10] were prepared as previously described by the reaction of the corresponding β-lactones with dimethytitanocene. Compound **1f** was prepared in the same manner from the known β-lactone 3,3-dimethyl-4,4-diphenyloxetan-2-one,[11] and the β-lactone[12] required for 2-methyleneoxetane **1d** was prepared by benzylation of **9**.[1]

Simmons and Smith disclosed the potential of iodomethylzinc iodide, generated *in situ* from the reaction of the zinc–copper couple with diiodomethane, for the cyclopropanation of alkenes in 1958.[13] Since then, a variety of more convenient and reproducible procedures for preparing the Simmons–Smith reagent have been described.[14,15] 2-Methylenetetrahydrofurans have been cyclopropanated,[16–18] most successfully by the Furukawa procedure (diethylzinc and a dihalomethane).[19] Thus, we anticipated that this modification might be best for the cyclopropanation of 2-methyleneoxetanes. Nevertheless, we were concerned about the effect of Lewis acidic by-products on the reactants and/or products.

Initially, diiodomethane and diethylzinc in Et_2O at −5 °C were treated with 2-methylene-3-phenyloxetane (**1a**). The reaction was then allowed to warm to room temperature and stirred for 2 h. 4-Oxaspiro[2.3]hexane **5a** was isolated in low yield, and GC/MS showed numerous by-products. However, when the reaction temperature was maintained between −5 and 0 °C for 4 h, the starting material disappeared and only the desired product was produced; further warming resulted in numerous products. Quenching the reaction after 4 h at 0 °C, followed by purification, provided **5a** in 83% isolated yield. This protocol proved to be efficient for other 2-methyleneoxetanes, as is evident from the results in Table 1.

To our knowledge, there has been no examination of the behavior of 4-oxaspiro[2.3]hexanes in the presence of Lewis or protic acids. The corresponding 4-oxaspiro[2.2]pentanes **10** are known to undergo smooth rearrangements to cyclobutanones **12**.[20] The reorganization is more rapid when R, R′ ≠ H, supporting the presumed intermediacy and subsequent rearrangement of a carbonium ion related to **11**.[21] Recently, another related system, a 5-oxaspiro[3.2]hexane **13** was reported to rearrange to cyclopentenone **14** when treated with LiI.[22] Also, 2-oxo-1-oxaspiro[3.2]hexanes **15** provided a complex mixture of products when treated with $BF_3 \cdot Et_2O$.[23] However, **15** did rearrange to lactones **16**–**18** when exposed to catalytic quantities of $Cu(acac)_2$, suggesting a cyclopropyl cationic species of some sort that rearranges, based both on the catalyst and on the nature of R. Oxetanes (4-membered rings containing O) do not open as readily as oxiranes (3-membered rings containing O). In light of this, if ring opening of **5** occurred in a fashion similar to that of **10**, the resultant carbocation would not have the immediate pathway of a facile



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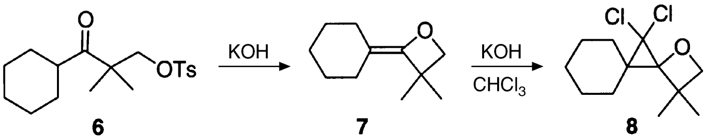
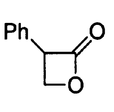


6 **7** **8**



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† Electronic supplementary information (ESI) available: full experimental details and characterization data for all previously unreported compounds. See http://www.rsc.org/suppdata/nj/b0/b010095l/

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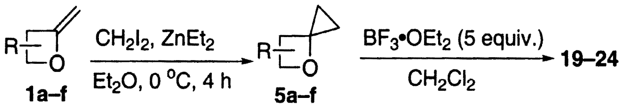
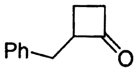
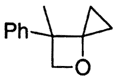
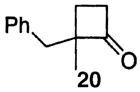
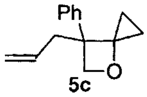
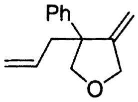
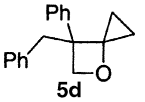
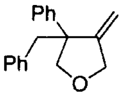
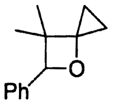
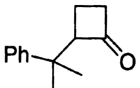
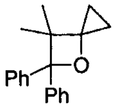
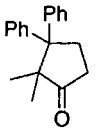
Table 1 Synthesis and reactions of 4-oxaspiro[2.3]hexanes



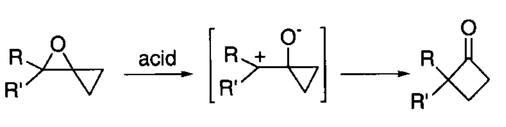
Oxaspirohexane	Isolated yield (%)	$BF_3 \cdot Et_2O$ conditions	Product	Isolated yield (%)
 **5a**	83	35 °C, 17 h	 **19**	35
 **5b**	87	35 °C, 17 h	 **20**	5
 **5c**	90	70 °C, 13 h	 **21**	7
 **5d**	82	35 °C, 35 h	 **22**	16
 **5e**	81	0 °C, 2 h	 **23**	48
 **5f**	98	0 °C, 2 h	 **24**	42

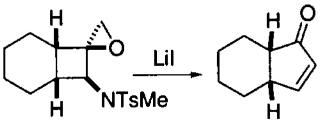
1,2-shift to an oxygen-stabilized carbonium ion. Thus, the fate of **5** is not easily predictable.

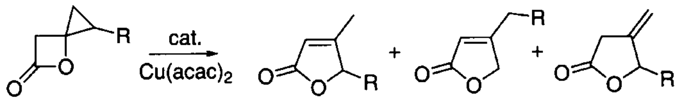
Our prediction that the 4-oxaspiro[2.3]hexanes **5** might not react as readily as the corresponding epoxides **10** was confirmed. When **5a** was treated with LiI and heated at reflux in THF for 24 h, the starting material was recovered. Conversely, oxaspirohexanes **5a–f** underwent rearrangements when treated with $BF_3 \cdot Et_2O$. However, the requirements for reaction and the outcome of the rearrangements varied significantly.

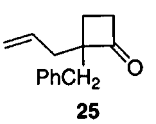
Cyclobutanones **19**, **20** and **23** (Table 1) were isolated from oxaspirohexanes **5a**, **5b** and **5e**, respectively. For compounds **5a** and **5e**, the indicated products were the only ones of significance in the crude reaction mixture, based on GC/MS. The rearrangement of **5b** was not as clean; however, cyclobutanone **20** was the major product in GC/MS traces. Oxaspirohexanes **5c** and **5d** gave a number of isomeric products, based on GC/MS. The predominant product in each case was the 4-methylenetetrahydrofuran (**21** and **22**). We were unable to separate **21** from one of its structural isomers.[12] Based on ^1H and ^{13}C NMR, it appears likely that this isomer is cyclobutanone **25**. Oxaspirohexane **5f** provided cyclopentanone **24** as the only product of significance seen in GC/MS traces.

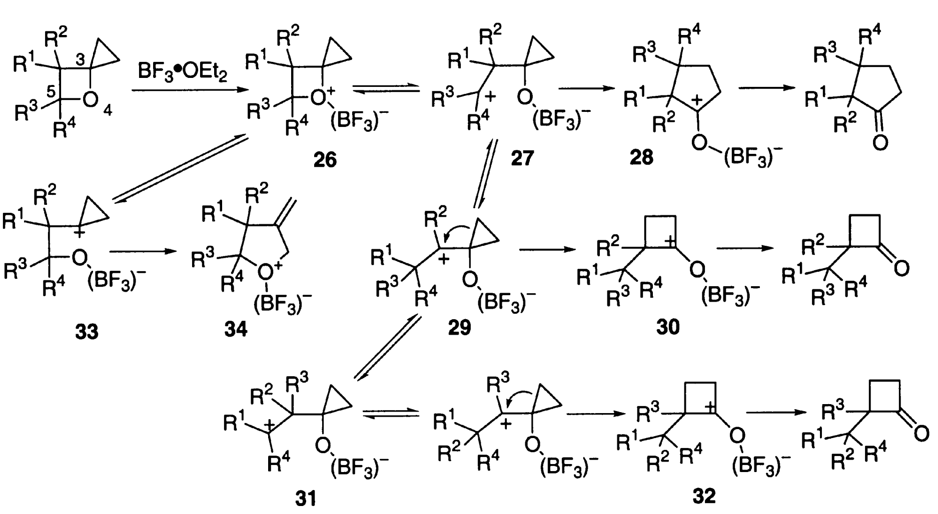
Initially, the divergent outcomes of the rearrangements were somewhat surprising. On further consideration, the results can be rationalized as shown in Scheme 2. Considering a generalized oxaspiro[2.3]hexane complexed to $BF_3 \cdot Et_2O$ (**26**), initial ring opening could occur in two directions. Cleavage at O4–C5 would provide carbocation **27**. A 1,3-bond migration involving the cyclopropane would then provide an oxygen-stabilized carbonium ion **28** that results in a cyclopentanone. Alternatively, **27** could undergo consecutive 1,2-shifts, ultimately leading to oxygen-stabilized cations **30** or **32** (*via* **29** or **31**, depending on the number of 1,2-shifts). If initial bond rupture occurred at O4–C3, the resulting cyclopropyl cation **33** would be expected to reorganize, and one possible product would be methylenetetrahydrofuran **34**. There are, obviously, other possible fates for the cations shown, and this could explain the low isolated yields. That the only cyclopentanone observed resulted from substrate **5f** suggests that only highly stabilized carbocations rearrange to the cyclopentanones. Even sub-











Scheme 2

strate **5e**, which would be expected to provide a relatively stable benzylic cation (see **27**), undergoes multiple 1,2-shifts, resulting in **23**. It is likely that in the formation of **19** and **20**, oxaspirohexanes **5a** and **5b** undergo phenyl migration concurrently with ring opening (equivalent to direct conversion of **26** to **29**). With **5a** the carbonium ion corresponding to **29** appears to be converted to the product in a reasonably efficient fashion. However, this is not the case with **5b**. The presence of other isomers was indicated by GC/MS, although we were unable to isolate any other clean, clearly identifiable products. It seems likely that both directions of initial rupture operate with **5c** and **5d**. Although 4-methylenetetrahydrodrofurans **21** and **22** were the products present in the largest yield, our observation of **25** in the rearrangement of **5c** confirms that initial O4–C5 cleavage also occurred.

The importance of the nature of the substituents in controlling reaction outcomes is further illustrated by the temperatures required for the reactions. Those substrates containing a phenyl at C5 provided products under the mildest conditions. The compounds lacking substitution at C5 required an elevated temperature for reaction. There was no improvement in results at an elevated temperature for the other oxaspirohexanes. Because of the involvement of multiple steps in going from reactant to product and the availability of alternative pathways, it is not surprising that the rearrangements of oxaspirohexanes occur with less efficiency and greater divergence in outcomes than the reorganizations of the corresponding oxaspiropentanes (see **10** to **12**).

In summary, we have demonstrated that oxaspirohexanes can be efficiently prepared from the corresponding 2-methyleneoxetanes using the Furukawa modification of the Simmons–Smith reaction. Preliminary studies of the reactivity of the oxaspirohexanes have shown that their behavior on exposure to $BF_3 \cdot Et_2O$ is governed by the nature of the substituents on the oxetane ring. Further studies are underway to see if the efficiency of any of these reactions can be improved by employing alternative Lewis acids or if the outcome can be more effectively controlled.

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