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Oxetan-3-ones from Allenes via Spirodiepoxides

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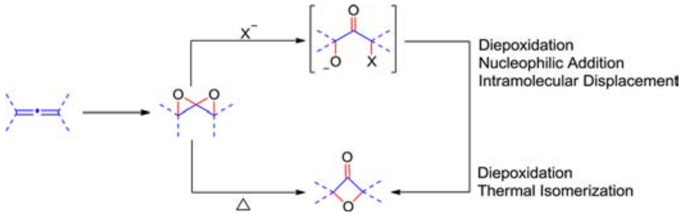
ABSTRACT



Two concise methods for generating oxetan-3-ones from allenes are reported. The first method employs allene epoxidation, opening of the spirodiepoxide by a halide nucleophile, and then intramolecular displacement of a halide by an alkoxide. The second method involves allene epoxidation and then thermal rearrangement of the corresponding spirodiepoxide to oxetan-3-one. The two methods are complementary and stereochemically divergent. Computational analysis of the thermal rearrangement is also described.

Oxetane containing compounds have many uses in synthetic and medicinal chemistry. Recently, Carreira and coworkers have used the oxetane moiety as a gem-dimethyl variant and to influence solubility, lipophilicity, metabolic stability, and molecular conformation.[1,2] Oxetan-3-ones are also useful in synthesis and drug discovery and can serve as precursors to oxetanes, as well as 3-aminooxetanes, oxetanocins, and other oxetane derivatives.[3] Steroids containing oxetan-3-ones have demonstrated antiinflammatory and antiglucocorticoid activities.[4,5] Owing to the considerable diversity of possible oxetan-3-one structural variants, new methods for the synthesis of these heterocycles are highly desirable. Routes to specific oxetanone targets and a limited number of methods for oxetanone synthesis are known.[3c,6] For example the recently described gold catalyzed oxidative cyclization of propargyl alcohols developed by Zhang is a marked advance over previous multistep routes.[6n] Nevertheless, tetra- and trisubstituted oxetan-3-ones that do not bear electron-withdrawing groups adjacent to the heterocycle are still difficult to access directly. We recognized that oxetan-3-ones and spirodiepoxides are isomers and there is the potential to use this precursor to access oxetan-3-ones. Two new methods that complement existing synthetic methods for this heterocycle are described below.

Allene double epoxidation gives spirodiepoxides. These synthetically useful intermediates allow direct entry to

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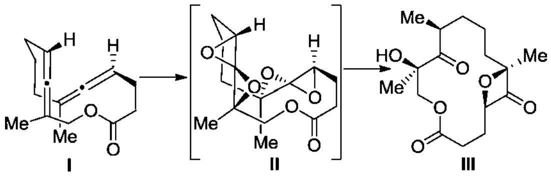
diverse motifs.[7] Although only one instance of the thermal rearrangement of this species to oxetan-3-ones has been described (by flash vacuum pyrolysis), oxetan-3-ones are commonly observed as byproducts of spirodiepoxide decomposition in acid.[7d,8] For example, we reported that epoxidation of bisallene **I** followed by exposure to lithium methylcyanocuprate gave oxetan-3-one **III** as a byproduct (Scheme 1).[7d]

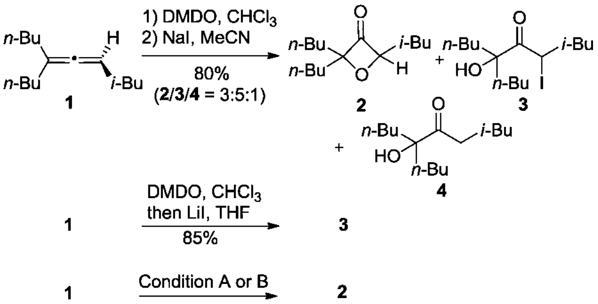
We have reported the synthesis of α-hydroxy-α′-haloketones from spirodiepoxides.[7a] It seemed reasonable that under similar reaction conditions the nascent alkoxide could be induced to displace the halide in situ and thereby form the oxetan-3-one.

Scheme 1. Oxetan-3-one Formation from Spirodiepoxide



We initially evaluated iodide (Scheme 2). Allene **1** was exposed to dimethyldioxirane (DMDO), and then the crude spirodiepoxide was taken up in acetonitrile. Subsequent addition of sodium iodide gave three products: the desired oxetan-3-one **2**, the α-hydroxy-α′-iodoketone **3**, and the α-hydroxylketone **4**. Lithium iodide gave iodohydroxylketone **3** as the sole product in good yield. The addition of HMPA to the lithium iodide reaction mixture gave the oxetan-3-one **2** (Scheme 2, condition A), as desired; however, these conditions were not generally effective for other substrates and often favored the hydroxyketone product. The ready loss of iodide from α-iodoketones is well-known.[9] Consequently, we turned to bromide and identified a simple, efficient, and reliable procedure for oxetan-3-one synthesis under mild conditions. Dissolution of the spirodiepoxide in tetrahydrofuran followed by addition of lithium bromide, replacement of the solvent with methyl sulfoxide, and then exposure to potassium hydroxide gave the oxetan-3-one (**2**) in excellent yield (92%, Scheme 2, condition B).

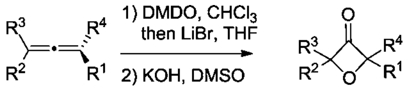
Scheme 2. Iodide Induced Oxetan-3-one Synthesis

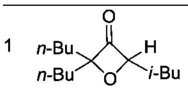
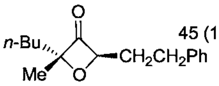
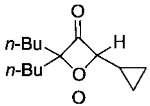
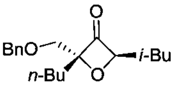
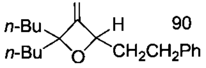
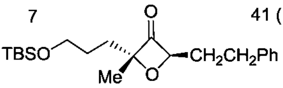
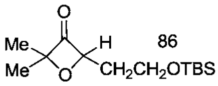


Condition A: DMDO, $CHCl_3$; LiI, THF then HMPA (76%)
Condition B: DMDO, $CHCl_3$; LiBr, THF; KOH, DMSO (92%)

We used this method to convert several allenes to oxetan-3-ones as shown in Table 1. For simple trisubstituted allenes the yields were excellent (Table 1, entries 1−4). However, for more complex trisubstituted allenes the yields were modest (Table1, entries 5−7). Importantly, the ratios of spirodiepoxide precursors and oxetan-3-one products were identical. The major byproduct was the simple hydroxyketone. Evidently, debromination competes with cyclization in some substrates.

Table 1. Bromide Induced Oxetan-3-one Synthesis[a]



entry	product	yield (%)	entry	product	yield (%), (dr)
1		92	5		45 (1.4:1)
2		93	6		41 (1.1:1)
3		90	7		41 (1.4:1)
4		86			

[a] Conditions: DMDO (2.5 equiv), $CHCl_3$, −20 °C, 1−2 h; LiBr (1.1 equiv), THF, 0 °C to rt, 1−3 h; KOH (1.10 equiv), DMSO, 5−10 min.

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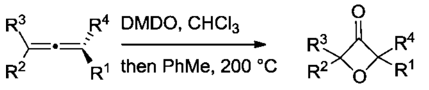
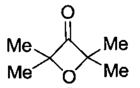
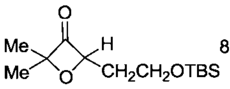
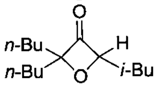
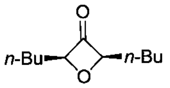
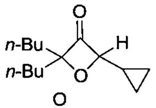
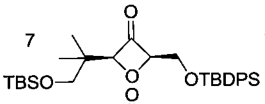
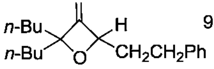
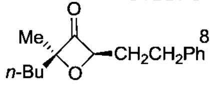
We also recognized that thermal rearrangement of the spirodiepoxide to the isomeric oxetanone represented an alternative approach. Spirodiepoxides have good kinetic stability in nonacidic conditions; they can be prepared in multigram scale, manipulated, and used without purification.[7] The data in Tables 2 and 3 demonstrate that these epoxides also have good stability to increased temperature. Initially, hot toluene (~100 °C) was used to effect rearrangement. For other substrates, higher temperatures were required and refluxing *p*-xylene worked well.[10] Further investigations demonstrated that microwave heating of spirodiepoxides at 200 °C effected their smooth and efficient rearrangement to oxetan-3-ones. This transformation was general for a range of allenes including tetrasubstituted (Table 2, entry 1), trisubstituted (Table 2, entries 2−5 and 8), and disubstituted (Table 2, entries 6 and 7) substrates. The moderate yield reported in Table 2, entry 1 is due to the high volatilities of the intermediate tetramethyl spirodiepoxide and the oxetan-3-one product. The diastereomeric ratio of allene epoxidation matched the ratio of oxetanones obtained (Table 2, entries 6 and 7). The stereochemical fidelity of the transformation suggests that rearrangement is concerted. A more complete mechanistic discussion is put forth below. The stereochemical assignments for the products in Table 2, entries 7 and 8 were based by analogy on findings for Table 2, entry 6. The assignment of entry 6 was determined unambiguously by reduction of the ketone (Scheme 3). Exposure of the major oxetan-3-one, **5**, to sodium borohydride gave two isomeric alcohols, **6** and **7**, whereas the minor oxetan-3-one, **8**, gave a single isomer **9**. These results are uniquely interpretable. The major oxetan-3-one must be the *cis* isomer as shown, with the products of reduction corresponding to the *cis* and *trans* alcohols (3.5:1). The minor oxetan-3-one must be the *trans* isomer; reduction of this compound can give only a single alcohol, since the hydroxyl-bearing carbon is not stereogenic.

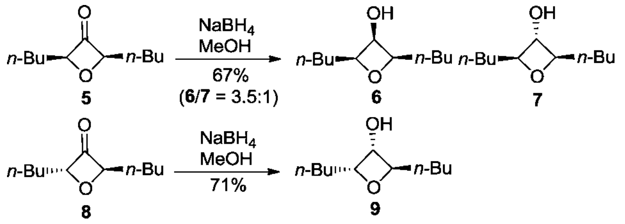
Table 2. Oxetan-3-one Synthesis by Thermal Rearrangement[a]



entry	product	yield (%)	entry	product	yield (%), (dr)
1		51	5		83
2		98	6		88 (2:1)
3		95	7		73 (8:1)
4		95	8		82 (1.4:1)

[a] Conditions: 2.50 equiv of DMDO, CHCl₃, −20 °C, 1−2 h; concd, PhMe, 200 °C, 1−1.5 h.

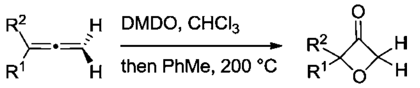
Scheme 3. Proof of Stereochemical Assignment

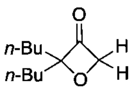
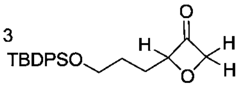
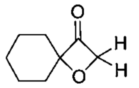
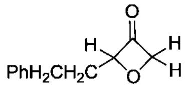


Spirodiepoxides derived from terminal allenes are particularly sensitive to manipulation, presumably due to the high accessibility of one of the reactive termini. Pleasingly, thermal rearrangement of these substrates was efficient (Table 3). Both acyclic and cyclic 1,1-disubstituted allene substrates were smoothly transformed to the corresponding terminal oxetan-3-ones (Table 3, entries 1 and 2), as were monosubstituted allenes (Table 3, entries 3 and 4). Indeed, the method summarized in Tables 2 and 3 provides a simple, single-flask procedure for the conversion of allenes to these functionalized heterocycles.

What are the stereochemical consequences of oxetan-3-one formation for these two methods? We reasoned that in the halide-induced method the spirodiepoxide is opened by a halide at the least substituted terminus with inversion at that substituted carbon (Scheme 4, top, **IV**→**V**). The bromide is then displaced by the alkoxide, and this same center is inverted again with overall retention (**V**→**VI**). Based on the stereochemical fidelity, we suggest that the thermal rearrangement method is a concerted, asynchronous one-step process. This pathway is expected to proceed with inversion of configuration on the carbon atom most able to stabilize the anticipated partial positive charge developed in

Table 3. Terminal Oxetan-3-one Synthesis by Thermal Rearrangement[a]



entry	product	yield (%)	entry	product	yield (%)
1		70	3		86
2		68	4		65

[a] Conditions: 2.50 equiv of DMDO, CHCl₃, −20 °C, 1−2 h; concd, PhMe, 200 °C, 1−1.5 h.

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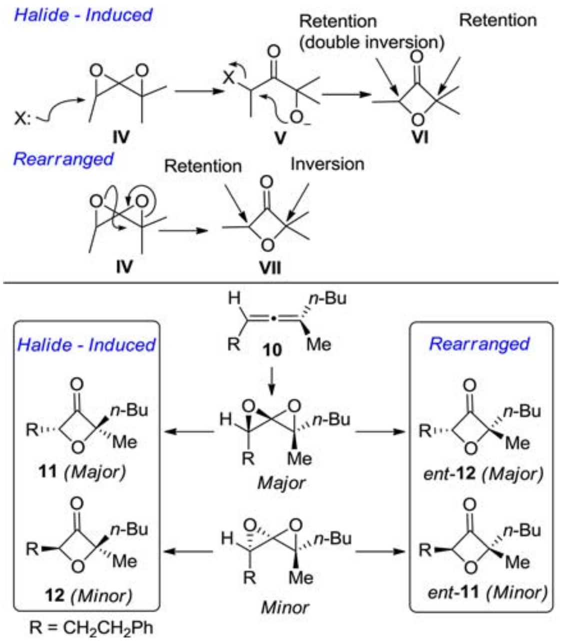
(10) In refluxing toluene, many spirodiepoxides failed to rearrange and only slow decomposition was noted after extended reaction times. See also ref 8f. High quality DMDO is especially important in the thermal rearrangement reaction; see Supporting Information in ref 7i for DMDO preparation.

Scheme 4. Mechanistic Framework



the transition structure. Taken together, the first method should engage the less substituted terminus of the epoxide, the second method should engage the more substituted terminus, and these methods should lead to divergent stereochemical outcomes.

These predictions are consistent with experimental findings (Scheme 4, bottom). Spirodiepoxides derived from enantioenriched allene **10** gave oxetan-3-one **11** and diastereomeric oxetan-3-one **12** as the major and minor products, respectively. In contrast, the major product of thermal rearrangement was the antipode of **12**, and the minor rearrangement product was the antipode of **11**. The two methods are highly complementary, as either diastereomeric oxetan-3-one can be prepared as the major product.[11]

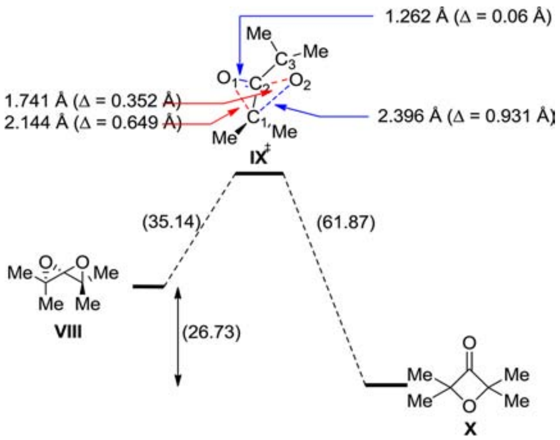


Figure 1. Computed concerted, nonsynchronous thermal rearrangement of spirodiepoxides to oxetan-3-ones. (All distances given in Å, differentials between starting material ground and transition state atomic distances given as Δ, energies given in kcal/mol.)[14]

We evaluated the thermal rearrangement computationally (Figure 1). Consistent with the experimental findings thermal rearrangement was found to be concerted and asynchronous. A single barrier separates the starting material from product, and the reaction is highly exothermic. Key bond lengths of the computed transition structure (**IX**‡) are indicated.[12] As the transition structure is approached, C^1–O^1 elongates, O^1–C^2 contracts, C^2–O^2 elongates, and O^2–C^1 contracts. Importantly, the C^1–O^1 bond distance increases by 0.649 Å without compensating the contraction between O^2 and C^1, indicative of a significant charge buildup on C^1.[13] This insight supports the above rationale and is consistent with the stereochemical data and mechanistic framework outlined in Scheme 4.

In summary, we have reported two methods of oxetan-3-one synthesis and have described key stereochemical and mechanistic features of these new reactions. Oxetan-3-ones can be accessed in one or two steps from allenes, which are readily prepared from commercial reagents. The methods allow access to structure types that are problematical for other procedures and thus complement previous methods of oxetanone synthesis.

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Supporting Information Available. Synthetic methods, compound characterization data, energies and coordinates for computed structures, and the full citation for ref 14a. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The first epoxidation of an allene effectively sets the absolute configuration of the SDE, as it converts the chiral axis to center chirality. The second epoxidation determines the diastereomeric ratio within that enantiomeric series. In the halide-induced method, both configurations are retained. In the thermal rearrangment the center that sets the absolute configuration is inverted, reversing the enantiomeric series. This is the only center that is inverted; consequently, the diastereotopicity is also reversed relative to the halide-based method.

(12) See Supporting Information for the full structural details of these calculations.

(13) (a) The frequency calculation of the transition structure revealed a vibrational mode similar to a vibrational mode in the SDE starting material. This relationship suggests a vibrational pathway that enables the concerted process. See: (b) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 10646. (c) Ess, D. H.; Houk, K. N. *J. Am. Chem. Soc.* **2008**, *130*, 10187. (d) Kolakowski, R. V.; Williams, L. J. *Nat. Chemistry* **2010**, *2*, 303 and references cited therein.

(14) (a) Electronic structure calculations were performed and optimized using DFT (B3LYP) and the G631* basis set: (a) Gaussian 03 (revision B.02): Frisch, M. J.; et al. ; see the Supporting Information. B3LYP functional: (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. 6-31g(d,p) basis sets: (d) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294. (e) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639. (f) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (g) Hariharan, P. C.; Pople, J. A. *Mol. Phys.* **1974**, *27*, 209. (h) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* 1971, *54*, 721. CPCM: (i) Cossi, M.; Barone, V. *J. Phys. Chem. A* **1998**, *102*, 1995.

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