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Preparation of Bicyclic 1,2,4-Trioxanes from γ,δ -Unsaturated Ketones

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Abstract

Treatment of γ,δ -unsaturated ketones with hydrogen peroxide and acid provides a rapid entry into the medicinally important 1,2,4-trioxane structure. Alkene substitution that stabilizes carbocationic intermediates proved to be important for the success of this transformation.

The 1,2,4-trioxane moiety of the sesquiterpene artemisinin (**1**, Figure 1) is considered to be an important component of the potent anti-malarial activity of this natural product.¹ Artemisinin and its semi-synthetic derivatives are some of the most successful drugs for the treatment of malaria.² Despite the effectiveness of artemisinin, malaria is still a worldwide epidemic responsible for millions of deaths annually, and strains of the *Plasmodium falciparum* parasite are growing increasingly resistant to older drug therapies.³ Development of new syntheses of organic peroxides could address many challenges associated with malaria treatment, such as drug resistance and availability.⁴ In addition to anti-malarial properties, organic peroxides, such as artemisinin, have notable activity against tumor cells⁵ and viruses like HIV⁶ and hepatitis B.⁷

In this Letter, we describe the efficient synthesis of 1,2,4-trioxanes **3** from simple γ,δ -enones **2** in one synthetic operation, without isolation of intermediates (Figure 2). This procedure complements the multi-step methods reported by Wu⁸ and Griesbeck⁹ because it enables access to 1,2,4-trioxanes with different substitution patterns.

The synthesis of 1,2,4-trioxanes **3** was discovered when we attempted to form *geminal*-dihydroperoxides from unsaturated ketones **2** (Figure 2). Treatment of γ,δ -unsaturated ketones with acidic hydrogen peroxide^{10,11,12,13} solutions gave the trioxane **3** and two identifiable decomposition products: peroxide oligomers¹⁴ and Baeyer-Villiger oxidation products.^{15, 16} Oligomerization was decreased by slow addition of the γ,δ -unsaturated ketone **2** into the reaction mixture. Lowering the reaction temperature reduced the amount of Baeyer-Villiger oxidation observed for a number of substrates.¹⁷ Finally, the addition of excess acid made a marked improvement in the efficiency of the reaction. For example, the yield of 1,2,4-trioxane **5** from γ,δ -unsaturated ketone **4** could be improved from 8% to 53% by making slight adjustments to the reaction conditions (Table 1).

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Supporting Information Available Complete experimental procedures and product characterization (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The formation of 1,2,4-trioxanes occurred most efficiently with acyclic aliphatic γ,δ -enones with trisubstituted alkenes. Ketoalkenes with short alkyl side-chains underwent the transformation most effectively, as shown by the formation of trioxanes **7**, **9**, and **11** (Table 2, entries 1–3). The synthesis of trioxanes **13** and **15** demonstrated that increasing the chain length and introduction of functional groups resulted in longer reaction times and decreased yields (Table 2, entries 4 and 5). If two different alkenes were present, only the more nucleophilic alkene¹⁸ was oxidized (Table 2, entry 4). Functionalized alkenes were also tolerated (Table 2, entry 6).

Attempts to extend the scope of the rearrangement to form trioxabicyclo[3.3.1]nonane **19** failed, instead leading to dioxabicyclo[3.2.1]octane **20** (eq 1). Others have encountered difficulties in forming trioxabicyclo[3.3.1]nonanes.^{8c}

(1)

Structural assignment of the products from these reactions required careful analysis (Scheme 1). Without authentic samples of structures **7** and **21**, both structures might be considered to be consistent with the ¹H NMR spectra. Two-dimensional NMR spectroscopy, however, could differentiate between these structures. A cross-peak between the bridgehead proton and acetal carbon was observed when the HMBC experiment was optimized for ¹H-¹³C coupling constants of 10 Hz. This result indicated that the structure of the rearrangement was the trioxabicyclo[3.2.1]octane **7**, and not trioxabicyclo[2.2.2]octane **21**. The proposed structure was later confirmed by X-ray crystallography.¹⁹

For the formation of 1,2,4-trioxane **3**, we propose the mechanism outlined in Scheme 2. Addition of hydrogen peroxide to the carbonyl group,^{13,20} followed by *in situ* epoxidation by trifluoroacetic peracid,²¹ would afford a mixture of epoxides **22** and **23**. Cyclization of the hydroxyl group of hemi-peroxyketal **23** would provide intermediate tetrahydrofuran **24**.²² Cyclization to give tetrahydrofuran **24** could also occur by hydrolysis of epoxide **22** or **23** to form a diol (not shown) followed by hemi-peroxyketalization.²³ The highly acidic conditions in the reaction mixture could promote the formation of cis and trans tertiary carbocations **25** and **26**. Ring closure to provide the 1,2,4-trioxane **3** occurs when the tertiary carbocation is generated and is in a cis relationship (intermediate **25**) with the anomeric hydroperoxide. Ring closure to afford the bicyclic 1,2,4-trioxane would not be expected to occur if the hydroperoxide and carbocation reside in a trans relationship, as seen in intermediate **26**.^{8c}

To test the viability of the suggested mechanism, intermediates were synthesized independently and subjected to the reaction conditions. Epoxy ketal **28** was obtained by treatment of ketoalkene **6** with aqueous hydrogen peroxide and cerium ammonium nitrate (CAN)²⁴ followed by epoxidation with dimethyldioxirane (Scheme 3).²⁵ Exposure of epoxy ketal **28** to acid with or without hydrogen peroxide produced trioxane **7**.¹⁹ These results show that geminal-dihydroperoxides like **22** (Scheme 2) are competent intermediates in the formation of trioxanes **3**.

The hydroperoxy ketal portion of the intermediates was necessary for the synthesis of 1,2,4-trioxanes. When the epoxide **29**²⁶ was subjected to the reaction conditions, none of the desired trioxane **7** was observed (Scheme 3). This result indicates that formation of the peroxy ketal or hemi-ketal (e.g., **22** or **23**, Scheme 2) before epoxidation is necessary for production of 1,2,4-trioxanes **3**.

In addition to synthesizing hypothesized intermediates and transforming them to 1,2,4-trioxanes, some products have been isolated from reaction mixtures that are consistent with the proposed mechanism. Treatment of epoxide **30** to the reaction conditions provided primarily decomposition. Protonation with a weaker Brønsted acid yielded the diastereomerically pure tetrahydrofuran **31** (eq 2), a product that is structurally related to intermediate **24** (Scheme 2).¹⁹ The isolation of the spirocyclic product **31** with an anomeric hydroperoxide suggests the formation of the tetrahydrofuran ring occurs prior to carbocation formation. The weaker acid is not likely to generate a tertiary carbocation (e.g., **25** or **26**, Scheme 2), so the reaction stops at the tetrahydrofuran stage.

(2)

The presence of a carbocationic intermediate was probed with a substrate bearing a 1,2-disubstituted styryl group.²⁷ The product ratio of the resulting trioxanes **34a/b** was independent of the diastereomeric ratio of the starting alkene **32** (Table 3). The observation that the stereochemical integrity of the alkene was not maintained in the product is consistent with carbocationic intermediates.²⁸

In conclusion, the reaction of trisubstituted γ,δ -unsaturated ketones with acidic hydrogen peroxide solutions afforded 1,2,4-trioxanes efficiently. This reaction is believed to occur by an *in situ* epoxidation, hemi-peroxyketalization, and ring closure onto a carbocationic intermediate. The stabilization of this carbocation (**25**, Scheme 2) is a critical feature for the success of this transformation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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33 (Table 3) conferred by the phenyl substituent allowed the product to form from a disubstituted alkene.

28. Loss of stereochemistry was also observed in trisubstituted alkene substrates (Table 2, entry 6).

Figure 1.
1,2,4-trioxanes.

Figure 2.
Synthesis of 1,2,4-trioxanes from γ,δ -unsaturated ketones

Scheme 1.
Two potential products.

Scheme 2.
Proposed mechanism for 1,2,4-trioxane formation.

Scheme 3.
Synthesis of proposed intermediates.

Table 1

Optimization of rearrangement.

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entry	conditions	Yield of 5 ^a
1	CF ₃ CO ₂ H (12 equiv), H ₂ O ₂ (8 equiv), CH ₂ Cl ₂ , 23 °C	8%
2	CF ₃ CO ₂ H (2 equiv), H ₂ SO ₄ (2 equiv), 50% H ₂ O ₂ (10 equiv), CH ₂ Cl ₂ , 0 °C	53%

^aYield based on purified reaction mixtures.

Table 2Synthesis of 1,2,4-trioxanes from γ , δ -enones: substrate scope.

entry	ketoalkene	product	yield ^a
1	6	7	95% ^b
2	8	9	67%
3	10	11	88%
4	12	13	25%
5	14	15	27%
6	16^c	17	51% ^d

^aBased on purified reaction mixtures.^bAs determined by ¹H NMR spectroscopic analysis of the product relative to CH₂Cl₂.^c90:10 mixture of *E/Z* alkenes.^d3:1 mixture of diastereomers.

Table 3Synthesis of 1,2,4-trioxanes **34a/b** from a 1,2-disubstituted alkene.^a

entry	substrate	<i>E/Z</i> ratio	overall yield of 34	ratio 34a/34b
1	32	64:36	21%	86:14 ^b
2	32	98:2	46%	90:10 ^c

^a Reagents and conditions: (a) H₂O₂ (50%), CF₃CO₂H, H₂SO₄, 0 °C, 24 h.^b As determined by ¹H NMR spectroscopic analysis of the unpurified reaction mixture.^c Ratio as determined by isolated yield.