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Regioselective oxidative cyclization of hydroxyalkenes to tetrahydrofurans catalyzed by methyltrioxorhenium

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Abstract

The oxidation of 5-hydroxyalkenes by hydrogen peroxide, when catalyzed by CH_3ReO_3 (MTO), leads to functionalized tetrahydrofurans. In these cases, no tetrahydropyran was formed. The results show that the first reaction between the substrate and a peroxorhenium species formed from, and in equilibrium with, MTO and peroxide, yields an epoxide. This intermediate was not detected, however, because cyclization occurred so rapidly. 6-Hydroxyalkenes were similarly but more slowly converted to tetrahydropyran alcohols. A 4-hydroxyalkene was epoxidized but not cyclized.

Keywords: Catalysis; Rhenium; Hydroxyalkene; Peroxide; Oxidation

1. Introduction

A number of natural products, such as polyether antibiotics, contain tetrahydrofuran rings [1]. Certain methods have been developed in recent years to synthesize these heterocycles. Among them, chromium [2–5], rhenium [6–8], and thallium [9,10] oxo reagents are known to induce the oxidative cyclization of monoalkenes, when tethered to a bishomoallylic alcohol. Chromium(VI)-induced *cis*-oxidative cyclizations of hydroxyalkenes are limited to tertiary alcohols [2–5]. Oxidative cyclization mediated by dirhenium heptoxide produces predominantly *trans*-tetrahydrofuranyl alcohols and is compatible with primary and secondary hydroxyalkenes [6–8]. Thallium acetate, nitrate, and trifluoroacetate induce cyclization of alkenols to tetrahydrofurans [9,10]. These catalysts, which include Re_2O_7, have also been used for the oxidative polycyclization of hydroxypolyenes [11–16]. Most of these studies have been directed towards the stereoselective synthesis of substituted tetrahydrofurans. The metal reagents must be taken in relatively high amount (1–3 eq relative to substrate) and the yields are only 50%–70%. Peroxy acids can also be used to induce this kind of reaction, but without stereoselectivity [17]. Since methyltrioxorhenium (CH_3ReO_3, abbreviated as MTO) has proven ability to catalyze peroxide oxidations [18–20], we decided to attempt its use in the

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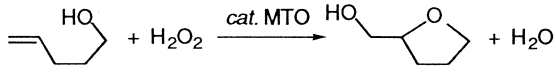
case at hand. Our goal was to produce THF derivatives by catalytic oxidation, such that there would be a remaining functional group, in this case CH_2OH, permitting further derivatization. We have attained that goal, and have developed a procedure for that transformation that proceeds with one experimental manipulation. When this work was in progress, we noted a reference to the use of MTO and hydrogen peroxide for the oxidative cyclization of 4-penten-1-ol to tetrahydrofurfuryl alcohol with MTO/H_2O_2, with 3-cyanopyridine added to stabilize the catalyst [18].

2. Results and interpretation

2.1. Catalysis by MTO

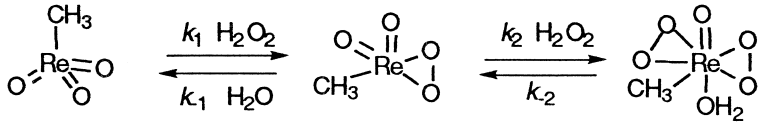
We have found that MTO functions as an efficient catalyst with hydrogen peroxide to make tetrahydrofurfuryl alcohols from 5-hydroxyalkenes. This method achieves nearly complete regioselectivity and has been used successfully with primary, secondary and tertiary 5-hydroxyalkenes. The net reaction for the parent 4-penten-1-ol is given by:



(1)

This reaction occurs to 100% conversion with 98% selectivity for this product under mild conditions. The first seven entries in Table 1 illustrate the same reaction for compounds with a methyl substituent on either position of the olefin or on the carbon bearing the OH group. These are reactions in which only a single geometric isomer of the product is possible. They went to 100% conversion, yielding the tetrahydrofurans with $>95\%$ selectivity. These examples show that an alkyl group on carbon does not alter the course of the reaction.

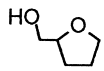
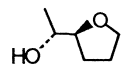
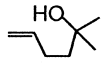
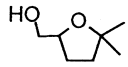
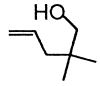
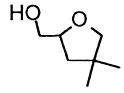
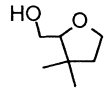
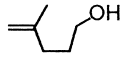
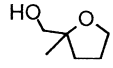
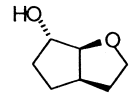
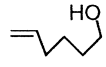
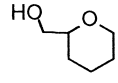
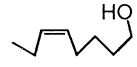
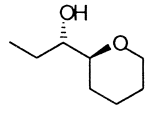
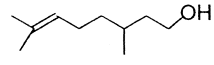
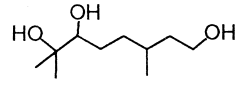
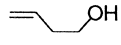
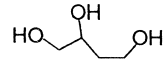
As to the mechanism followed, MTO-catalyzed reactions of hydrogen peroxide are well known [19–22]. The active forms of MTO are its monoperoxo and diperoxo complexes, designated A and B, respectively [19]:



MTO A B

MTO-catalyzed reactions, epoxidations in particular, have been thoroughly documented [23–27]. Comparison of these results to the earlier data allows us to conclude that epoxidation occurs in the initial stage of reaction between the substrate and A or B. The relative contributions of A and B depend on the concentration of hydrogen peroxide. Indeed, the epoxidation step is rate-controlling, because no epoxide buildup was evident in the ^1H spectra taken throughout the reaction. This shows that the epoxide was consumed in a faster step. In support of that, we note that the less substituted alkenes are the least reactive, as judged by the required reaction times in Table 1. The same trend has been independently determined for epoxidations [23–25]. This reactivity order simply reflects the established trend that the more alkyl substituents on a double bond, the higher the rate; terminal alkenes that lack a methyl group on the double bond are thus the least reactive.

Table 1
Products[a] of the MTO-catalyzed oxidative cyclization of hydroxyalkenes

Entry	Reactant	Product [b]	Yield (%)	Rxn time/h
1			98	6
2			95	3
3			96	6
4			95	6
5			97	6
6			98	2
7			95	2
8			82 [c]	10
9			97	5
10			93	2
11			90	2

[a] A single enantiomer is shown for entry 7; a D,L-mixture was formed.
[b] Products 1, 8 and 11 are commercially available. The following compounds are known compounds; their NMR and mass spectra matched the data given in the references cited: Entries 2 [29], 3 [30], 5 [31], 6 [32], 9 [30], 10 [33], 12 [34,35], 13 [36,17], 14 [37,38], 15 [39–42], 16 [43], 18 [13], 19 [13], 20 [44,45], and 21 [46].
[c] The balance is the triol.

Another experiment was done in acetonitrile with urea–hydrogen peroxide instead of 30% aqueous hydrogen peroxide [25]. 5-Hexen-1-ol could be oxidized to 5,6-epoxy-1-hexanol in 12 h. Then, 0.20

M perchloric acid was added and tetrahydropyran-2-methanol was isolated in 92% yield. For 4-penten-1-ol, however, the ring-closing reaction was much faster and the only product with urea–hydrogen peroxide was tetrahydrofurfuryl alcohol.

2.2. Ring formation

Intramolecular nucleophilic substitutions occur in a kinetic order depending on the size of the resulting ring: $5 \gg 6 > 3 > 7 > 8$ [28], and the relative rates for forming five- and six-membered rings could differ by 10^3. In accord with these trends, the present set of cyclization reactions shows excellent regioselectivity for the formation of a five-membered ring (Table 1), although the reactions could conceivably have produced six-membered rings (in Eq. (1), for example, 2-hydroxy-oxacyclohexane might instead have been formed). Thus, the ring preference here is again $5 \gg 6$. Related to this are the homologous systems, entries **8** and **9**, which are 6-hydroxyalkenes. In these cases, the products, which are tetrahydropyran alcohols, do have six-membered rings. Entry **10** might have closed to a seven-membered ring, but this is so disfavored that only the triol was obtained. When a 4-hydroxyalkene (entry **11**) was used, no oxidative cyclization occurred, and a triol resulted here as well. These triols are simply the product of the acid-catalyzed ring opening of epoxy alcohols.

2.3. Isomers

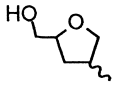
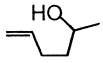
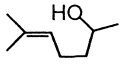
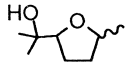
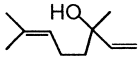
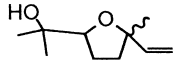
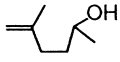
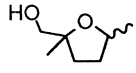
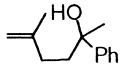
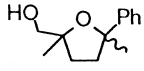
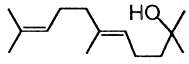
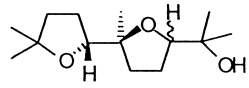
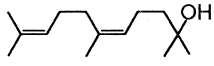
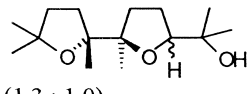
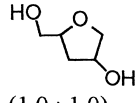
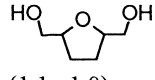
No selectivity was found for the production of *cis*- vs. *trans*-geometric isomers (Table 2). When an alkyl group is bound to a carbon atom that becomes part of the ring, then *trans* and *cis* isomers are formed. These two are usually produced in comparable yield; such cases are not likely to be useful in synthesis.

Appropriately constituted hydroxydienes (entries **18** and **19**) undergo ring formation twice, producing a bistetrahydrofuranyl alcohol. These two examples differ from one another only as regards the geometric isomers of the starting material at the central double bond; they gave geometric isomers of the products. Nonconjugated dienes (entries **20** and **21**) differ from conjugated dienes [25], in that only one double bond could be oxidized. The nonconjugated dienes were oxidized very slowly in $CHCl_3$. When the solvent was changed to CH_3CN, however, both double bonds were oxidized leading to the hydroxy tetrahydrofuran.

3. Experimental

The general procedure employed a scale of 0.4–4 mmol of the hydroxyalkene, which was sufficient to allow the product to be isolated in usable amount and pure form. The reactions were carried out under neutral conditions at room temperature using 30% hydrogen peroxide. The general procedure is this: 0.4 mmol substrate in 1.0 ml chloroform was treated with 20 μmol MTO and 0.5–1 mmol H_2O_2. The two-phase mixture was stirred at room temperature for the necessary reaction time. At the completion of the reaction, Na_2CO_3 was added to decompose MTO. The product was extracted with ether and washed with a small amount of water. To shorten the reaction time, the heterogeneous mixture of 4-penten-1-ol was stirred at 40°C for 1 h. The product yields shown in Table 1 were obtained with this procedure. Comparable results were obtained when 10 times as much substrate and 100 μmol MTO. were used; the level of MTO could be lowered further at the cost of a longer reaction time.

Table 2
Isomeric products of the MTO-catalyzed oxidative cyclization of alkyl-substituted hydroxyalkenes

Entry	Reactant	Product (cis:trans)	Yield(%)	Rxn time/h
12		 (0.85 : 1.0)	96	6
13		 (0.82 : 1.0)	95	6
14		 (1.6 : 1.0)	92	1
15		 (0.86 : 1.0)	92	1
16		 (1.0:1.4)	97	2
17		 (1.0 : 1.0)	94	1
18		 (0.81 : 1.0)	91	2
19		 (1.3 : 1.0)	90	2
		10		
20[a]		 (1.0 : 1.0)	72	12
21[a]		 (1.1 : 1.0)	70	12

[a]The reaction was carried out in CH_3CN, and the by-products were diol and tetraol.

The stereochemistry was verified from the ^{1}H NOE spectra, and the *cis*:*trans* ratio determined by integration of the NMR and GC. The products are mostly known compounds, the identities of which were confirmed by matching NMR and mass spectrometric data. Three compounds were new: entries **4**, **7**, and **17**. Their high resolution mass spectra were used for identification purposes; in every case, there was an exact match of molecular weights. Their spectroscopic data are as follows.

*3.1. (4,4-Dimethyl-tetrahydrofuran-2-yl) methanol (**4**)*

^{1}H NMR ($CDCl_3$) δ, ppm: 4.15–4.19 (m, 1H), 3.63–3.69 (m, 1H), 3.48–3.54 (m, 3H), 1.57–1.73 (m, 1H), 1.44–1.52 (m, 1H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR: 80.04, 79.85, 65.09, 41.94, 39.71, 26.44, 26.06; MS(EI) m/z: 130 ($M^{\#}$, 98%), 113 (62%), 99 (40%), 95 (100%). HRMS calculated for $C_7H_{14}O_2$ 130.09937, found 130.09937.

*3.2. 6#Hydroxy-hexahydro-cyclopenta⟨b⟩furan (**7**)*

^{1}H NMR ($CDCl_3$) δ, ppm: 4.15–4.18 (m, 2H), 3.66–3.81 (m, 2H), 2.75–2.89 (m, 1H), 1.40–2.17 (m, 6H); ^{13}C NMR: 90.85, 77.74, 68.57, 41.21, 34.01, 32.50, 29.81; MS(EI) m/z: 128 (M^+, 23%), 111 (15%), 83 (100%). HRMS calculated for $C_7H_{12}O_2$ $(M - CH_3)^+$ 128.08373, found 128.08367.

*3.3. (2,5-Dimethyl-5-phenyl-tetrahydrofuran-2-yl) methanol (**17**)*

Cis: ^{1}H NMR ($CDCl_3$) δ, ppm: 7.39–7.46 (m, 2H), 7.29–7.34 (m, 2H), 7.18–7.25 (m, 1H), 3.35–3.45 (m, 2H), 2.01–2.25 (m, 3H), 1.57–1.60 (m, 1H), 1.50 (s, 3H), 1.36 (s, 3H); ^{13}C NMR: 148.73, 128.30, 126.54, 124.68, 85.29, 68.92, 38.77, 33.42, 31.91, 24.02; MS(EI) m/z: 207 ($M^+ - 1$, 2%), 191 (8%), 175 (100%), 157 (33%). HRMS calculated for $C_{12}H_{15}O_2$ $(M - CH_3)^+$ 191.10720, found 191.10725. *Trans*: ^{1}H NMR: 7.39–7.46 (m, 2H), 7.29–7.34 (m, 2H), 7.18–7.25 (m, 1H), 3.46–3.58 (m, 2H), 2.15–2.40 (m, 3H), 1.79–1.94 (m, 1H), 1.53 (s, 3H), 1.20 (s, 3H); ^{13}C NMR: 149.17, 128.00, 126.32, 124.37, 85.25, 69.47, 39.53, 33.97, 31.23, 24.93; MS(EI) m/z: 207 ($M^+ - 1$, 2%), 191 (7%), 175 (100%), 157 (31%). HRMS calculated for $C_{12}H_{15}O_2$ $(M - CH_3)^+$ 191.10720, found 191.10725.

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