Chemistry of 1,2,4-Trioxanes: Metal-Induced Deoxygenation and Rearrangement of the 1,2,4-Trioxane Obtained by Photooxidation of β-Ionone

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Abstract: The reactivity of 2,2,6,8-tetramethyltricyclo[6.2.2.01,6]dodecene (2) toward different metal salts has been explored. In the presence of Fe(II), Sn(II) and Ce(IV) ions, compound 2 underwent a rearrangement process to afford acyclic triketones 3 and 4. The action of Zn powder in acetic acid resulted in an unexpected formation of furan 5 in high yield.

Key words: peroxides, trioxanes, furans, rearrangements, deoxygenation

During the last few years, there has been a renewed interest in the chemistry of cyclic peroxides and related compounds, stimulated by the strong pharmacological activities exhibited by several natural products which have a cyclic peroxide unit incorporated into their structure. A remarkable example is the potent antimalarial artemisinin (1) (Figure 1), the first natural occurring 1,2,4-trioxane, totally different from previous antimalarials in its structure and mode of action. This has led to great interest in the chemistry, drug development, and mechanism of action of this novel class of antimalarial agents. The peroxo group is essential for the biological activity and it is currently believed that the cleavage of the endoperoxide linkage of the 1,2,4-trioxane ring caused by Fe(II) is the initial step in the parasiticidal action. Several proposals of how the resultant oxyl radicals react to form cytotoxic intermediates have been suggested.

![Figure 1](attachment://Figure_1.png)

In addition to considerations of their biological activity and structural novelty, cyclic peroxides of various types are known to undergo versatile chemical transformation and have been employed as key intermediates for creating a variety of dioxygen substituted substances by cleavage of the oxygen–oxygen bond with high degree of stereo- and regioselectivity. Within this context, the 1,2,4-trioxane unit has been virtually unknown as a chemical class, and its chemical behaviour has been less extensively explored. Studies on their fragmentation by thermolysis have been reported and their selective transformation into 1,2-diols and 1,2-diol-monoesters demonstrated that they have synthetic potential.

In connection with our work on the synthesis of 1,2,4-trioxanes derived from the photooxidation of β-ionone type compounds, and taking into account the growing interest in the reactivity of these systems, not only related to biological aspects, but also in view of the potential value of products to be obtained, we decided to examine the chemistry of these peroxidic compounds. In this study, compound 2 was selected as a representative substrate and its behavior versus several oxophilic reagents under a variety of conditions was tested (Scheme 1).

In the first instance, the reactivity of 2 was examined in the presence of Fe(II) and Zn in glacial acetic acid, since the action of these reagents on 1 and related compounds have been investigated in connection with their antimalarial activity. The obtained results are summarized in the Table.

The treatment of 2 with Fe(II) sulfate produced an extensive fragmentation of the trioxane ring giving the triketone Z-3 in moderate yield (Scheme 1, Table). The influence of solvent on the course of the reaction was tested with little effect on either product ratio or yield (Entries 1 and 2). On the other hand, on prolonging the reaction time, the yield of Z-3 was only moderate although the starting trioxane was entirely consumed (Entry 3). When 2 was allowed to react with 5 equivalents of Fe powder in a mixture of aqueous acetic acid, Z-3 was obtained in 70% yield (Entry 4). The better source of divalent iron ion provided by this system may account for the improvement of the yield of Z-3.

We then examined the effect of Zn in acetic acid, a reagent that is known to deoxygenate 1,2,4-trioxanes such as 1, affording the corresponding 1,3-dioxolanes. Treatment of 2 with Zn in aqueous acetic acid led to the production of the furan 4 as the only product in 80% yield, instead of the expected 1,3-dioxolane 5 (Entry 5). Furthermore, no reaction occurred when trioxane 2 was treated with typical peroxide-cleaving reagents like triphenylphosphine or...
thiourea (Entries 6 and 7). The same particular stability of the peroxide bond toward this type of reagents is in agreement with previous studies on other 1,2,4-trioxanes.9a,b

The generation of Z-3 from interaction of 2 with Fe(II), can be attributed to the cleavage of the peroxo bond due to an electron transfer with the generation of an oxygen-centered radical. In accord with the mechanisms suggested for the analogous ferrous-induced degradation of endoperoxidic compounds,13 subsequent β-scission reactions would account for the formation of Z-3 (Scheme 2).

Scheme 1

Scheme 2

Table  Reactions of 1,2,4-Trioxane 2 with Oxophilic Reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent (equiv)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Reaction time (h)</th>
<th>Products and Yield (%) a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeSO₄ (2)</td>
<td>MeCN–H₂O</td>
<td>r.t.</td>
<td>4</td>
<td>Z-3 (20), 2 (40)</td>
</tr>
<tr>
<td>2</td>
<td>FeSO₄ (2)</td>
<td>THF</td>
<td>30</td>
<td>4</td>
<td>Z-3 (30), 2 (40)</td>
</tr>
<tr>
<td>3</td>
<td>FeSO₄ (2)</td>
<td>THF</td>
<td>r.t.</td>
<td>24</td>
<td>Z-3 (45)</td>
</tr>
<tr>
<td>4</td>
<td>Fe (5)</td>
<td>AcOH–H₂O–THF</td>
<td>r.t.</td>
<td>1.5</td>
<td>Z-3 (70)</td>
</tr>
<tr>
<td>5</td>
<td>Zn (10)</td>
<td>AcOH–H₂O–THF</td>
<td>r.t.</td>
<td>2</td>
<td>4 (80)</td>
</tr>
<tr>
<td>6</td>
<td>Ph₃P (2)</td>
<td>Cl₂CH₂</td>
<td>r.t.</td>
<td>48</td>
<td>NR b</td>
</tr>
<tr>
<td>7</td>
<td>thiourea (2)</td>
<td>MeOH</td>
<td>r.t.</td>
<td>48</td>
<td>NR b</td>
</tr>
<tr>
<td>8</td>
<td>SnCl₂·2H₂O (1)</td>
<td>Cl₂CH₂</td>
<td>0</td>
<td>3</td>
<td>Z-3 (20), E-3 (30), 2 (20)</td>
</tr>
<tr>
<td>9</td>
<td>SnCl₂·2H₂O (1)</td>
<td>Cl₂CH₂</td>
<td>-10</td>
<td>8</td>
<td>E-3 (50)</td>
</tr>
<tr>
<td>10</td>
<td>CAN (1)</td>
<td>MeCN</td>
<td>r.t.</td>
<td>24</td>
<td>Z-3 (10), E-3 (40)</td>
</tr>
<tr>
<td>11</td>
<td>CAN (0.5)</td>
<td>MeCN</td>
<td>r.t.</td>
<td>36</td>
<td>Z-3 (30), E-3 (20), 2 (15)</td>
</tr>
<tr>
<td>12</td>
<td>Ce(SO₄)₂ (2)</td>
<td>CHCl₃</td>
<td>r.t.</td>
<td>144</td>
<td>E-3 (60)</td>
</tr>
</tbody>
</table>

a Yield of chromatographically purified products.
b No reaction.
While the Fe(II)-induced decomposition of peroxides has been explained by one-electron transfer process, the reaction of 1,2,4-trioxanes with Zn powder in acetic acid has been rationalized by the oxophilic nature of Zn and insertion of an Zn atom into the O–O bond. In this line, the mechanism by which furan 4 is formed appeared to be complex, involving not only a deoxygenating reaction but also a rearrangement process. To obtain more insight into the furan formation and to compare the reactivity of the unsaturated 1,2,4-trioxane unit with the saturated one, compound 2 was reduced to provide the saturated 1,2,4-trioxane 6 by catalytic hydrogenation\(^{12}\) (Scheme 1). Treatment of compound 6 with Zn powder in analogous conditions, gave the 1,3-dioxolane 7, in 75% yield (Scheme 1). This contrastive result strongly suggested the involvement of the double bond of 2 in the generation of 4. A control experiment showed that triketone Z-3 would not be implicated in the formation of 4. The treatment of Z-3 with Zn powder in the same conditions, for three days, afforded the triketone 8,\(^{14}\) corresponding to the reduction of the double bond of 2, in low yield (Scheme 3). Related selective reduction of the C=C bond in \(\alpha,\beta\)-unsaturated \(\gamma\)-dicarbonyl compounds promoted by Zn powder in acetic acid has been reported.\(^{15}\)

![Scheme 3](image)

Scheme 3

Based on these results a probable mechanism for the formation of the observed products is shown in Scheme 4. The deoxygenation of 6 is initiated by the insertion of an Zn atom into the O–O bond to generate a metallacycle intermediate 9, which then extrudes an oxygen atom to afford 7. A parallel mechanism can be proposed for the conversion of 2 into furan 4. Compound 2 is deoxygenated to give dioxolane 5, which undergoes a rapid rearrangement, which might formally be attributed to a retro Diels–Alder process.

It is known that substituted 1,2-dioxines can be transformed into furans by the action of Fe(II)\(^{16}\) and Co(II)–tetraphenylporphrin.\(^{17}\) The present transformation of 2 into 4 promoted by Zn may constitute a complementary route to obtain furan compounds.

As a complementary study, and to test the 1,2,4-trioxane unit as a dual protecting group, liberating the 1,2-diol together with the corresponding carbonyl group,\(^{18}\) 2 was treated with low valent tin chloride\(^{19}\) and Ce(IV) salts,\(^{20}\) recently exploited for the deprotection of acetals. The expected deprotection did not occur. Tin(II) chloride not only promoted the fragmentation process at short reaction time and low temperature, but also induced the rearrangement of Z-3 to the E-isomer E-3 (Scheme 1). In this case, the selectivity profile is different from the related Fe(II)-promoted reaction and the yields of Z-3 and E-3 were a function of the reaction time and temperature (Entries 8 and 9, Table). Surprisingly, Ce(IV) ion behaved similarly with 2, but compounds Z-3 and E-3 were obtained at longer reaction times (Entries 10–12). The rearrangement promoted by Ce(IV) ions can be attributed to its powerful nature as a Lewis acid,\(^{20}\) that provide low energy pathways for activation of the 1,2,4-trioxane unit toward the rearrangement process.

In summary, the reactivity of compound 2 has been explored toward different metal ions obtaining triketones Z-3 and E-3 as a consequence of a rearrangement process. As might be expected, the peroxy bond was the reactive moiety. In addition, by changing the metal ion, it is possible to selectively enhance formation of the triketone Z-3 or E-3. Exposure of 2 to the specific reductive conditions originated by Zn in aqueous acetic acid resulted in the formation of 4, that seems particularly interesting as an easy entry into substituted furan compounds. This chemistry demonstrates that the 1,2,4-trioxane unit can acts as a precursor of a variety of organic compounds, allowing the preparation of new oxygenated systems and also the preparation of known compounds which are obtained in better yields by a more convenient pathway. To confirm this particular reactivity, and evaluate its scope and limitations, work is in progress to extend this study to a series of substituted 1,2,4-trioxanes.

IR spectra were recorded on a Beckman Acculab 8 spectrometer. The \(^1\)H and \(^13\)C NMR spectra were measured at 200.1 and 50.3 MHz on a Bruker AC 200-E NMR spectrometer in CDCl\(_3\) solutions, with TMS as internal standard. Column chromatography was performed...
on silica gel 60H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc as hexane as solvent. Analytical TLC was carried out using Kieselgel Merck GF254 of thickness 0.20 mm. EI-mass spectra were performed by UCR Mass Spectrometry Facility, Riverside CA, USA.

Compounds Z-3, E-3, 4, 6 and 8 have been reported previously. Photolysis of 5,6-epoxy-5,6-dihydro-3-trioxane which have not been reported previously, gave the correct CH X

reported before. The 13 C NMR data for compounds Z-3, E-3, 4 and 8 in low yield.10,11 The furan 4 and triketone 8 have also been synthesized from 5,6-dihydroxy-5,6-dihydro-furo.14

Thermolysis of 2 gave E-3 in 50% yield.12 Compound 6 was obtained by catalytic hydrogenation or diimide reduction of 2. The 1H NMR data for Z-3, E-3, 4, 6 and 8 are in agreement with those reported before. The 13 C NMR data for compounds Z-3 and 6, which have not been reported previously, gave the correct CH X

multiplicities of C-resonances based on standard 13 C NMR experiments (fully decoupled and DEPT). The same analysis carried out for compounds E-3 and 8 led to a new assignment of their 13 C NMR data. Compound 7 has not been reported.

Metal-Induced Rearrangement; General Procedure

To a solution of trioxane 2 (100 mg, 0.44 mmol) in the corresponding solvent (10 mL), the required amount of the appropriate metal salt was added. The mixture was stirred at a set temperature (see Table for details). At the end of the reaction (monitored by TLC), the reaction mixture was filtered over Celite and washed with the appropriate solvent. The residue was purified by column chromatography providing pure products Z-3 and E-3.

(Z)-6,6-Dimethyl-3-undecen-2,5,10-trione (Z-3)

1H NMR: δ = 1.17 (s, 6 H, 2 CH3), 1.46–1.53 (m, 4 H), 2.12 (s, 3 H, CH3), 2.28 (s, 3 H, CH3), 2.37–2.43 (m, 2 H), 6.33 (d, 1 H, J = 12 Hz), 6.57 (d, 1 H, J = 12 Hz).

13 C NMR: δ = 18.51 (t), 23.47 (q), 23.47 (q), 29.21 (q), 29.56 (q), 38.48 (t), 43.39 (t), 46.39 (s), 130.42 (d), 139.12 (d), 201.4 (s, C=O), 206.0 (s, C=O), 208.13 (s, C=O).

(E)-6,6-Dimethyl-3-undecen-2,5,10-trione (E-3)

1H NMR: δ = 1.17 (s, 6 H, 2 CH3), 1.40–1.57 (m, 4 H), 2.11 (s, 3 H, CH3), 2.38 (s, 3 H, CH3), 2.36–2.44 (m, 2 H), 6.98 (d, 1 H, J = 15Hz), 7.30 (d, 1 H, J = 15 Hz).

13 C NMR: δ = 18.51 (t), 23.38 (q), 23.38 (q), 28.57 (q), 29.56 (q), 38.19 (t), 43.28 (t), 46.80 (s), 132.52 (d), 137.12 (d), 197.72 (s, C=O), 203.70 (s, C=O), 207.81 (s, C=O).

6-Methyl-6-(5-methyl-2-furyl)-heptan-2-one (4)

The substrate 2 (100 mg, 0.44 mmol) was dissolved in a mixture of THF (10 mL), glacial AcOH (1 mL), and H2O (1 mL) and (250 mg, 10 equiv) of powder zinc was added. The resulting mixture was stirred for 2 h at r.t. The reaction mixture was diluted with EtOAc (10 mL) and filtered over Celite. The organic layers were washed sequentially with H2O, sat. aq NaHCO3, and brine and dried (MgSO4). After removal of the solvent, the residue was purified by column chromatography obtaining the furan 4.

Yield: 80%.

1H NMR: δ = 1.22 (s, 6 H, 2 CH3), 1.40–1.52 (m, 4 H), 2.09 (s, 3 H, CH3), 2.24 (s, 3 H, CH3), 2.32–2.39 (m, 2 H), 5.81 (br s, 2 H).

13 C NMR: δ = 13.36 (q), 19.03 (t), 26.57 (q), 26.57 (q), 29.50 (q), 35.30 (s), 41.13 (t), 43.90 (t), 103.69 (d), 105.25 (d), 149.79 (s), 160.57 (s), 209.01 (s, C=O).

An identical procedure was used for the conversion of the saturated trioxane 6 into dioxyolane 7.

2,2,6,8-Tetramethyl-7,9,10-trioxatricyclo-(6.2.2.01,6)dodecane (6)

1H NMR: δ = 0.96 (s, 3 H, CH3), 0.98 (s, 3 H, CH3), 1.05–1.18 (m, 1 H), 1.26 (s, 3 H, CH3), 1.41 (s, 3 H, CH3), 1.48–1.80 (m, 4 H), 1.95–2.19 (m, 5 H).

13 C NMR: δ = 19.22 (t), 19.69 (t), 23.26 (q), 24.63 (q), 25.72 (q), 25.87 (q), 30.00 (t), 35.78 (t), 36.40 (t), 37.19 (s), 77.91 (s), 80.63 (s), 96.70 (s).

2,2,6,8-Tetramethyl-7,9-dioxatricyclo-(6.2.2.01,6)dodecane (7)

Colorless oil.

IR (film): 2920, 1450, 1390, 1180, 920 cm–1

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References

(11) This yield is a great improvement compared with that previously reported10 (3% yield).