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The Formation of a Peracetal and Trioxane from an Enol Ether with Copper(II) Triflate and Oxygen: Unexpected Oxygenation of Aldol Intermediates

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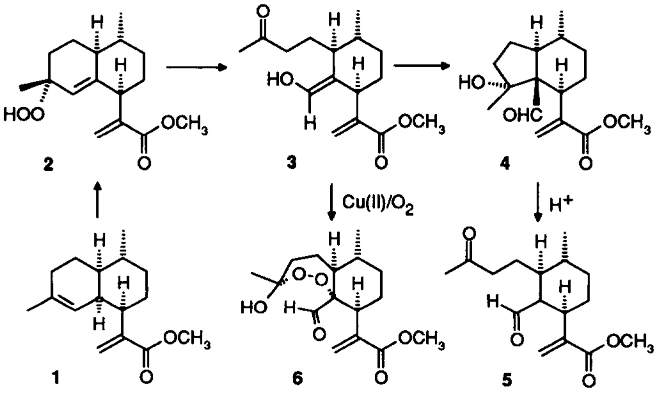
Abstract: The enol ether **7** undergoes rapid conversion into a 2:3 mixture of cis aldol **9** and trans aldol **11** in the presence of copper(II) triflate (0.1 equiv) and water (1 equiv) in MeCN with no intermediate formation of the corresponding ketoaldehyde **12**. In the presence of oxygen, slow oxygenation of the aldols takes place to give the peracetal **13** and trioxane **14** (93:7, 47% combined yield), and the methoxyaldehyde **8** in 12% yield. It is proposed that retroaldolisation to an enol or Cu(II) enolate which is oxidised to an enol radical is the key step. Oxygenation of trans aldol **11** with Cu(II)/O_2 in the presence of MeOH gave the peracetal (37%), trioxane (2%), and the methoxyaldehydes **8** (4%) and **10** (4%). The cis aldol **9** reacted, by comparison, very slowly under the same conditions.

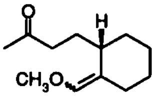
Recently, we established that under nitrogen in MeCN in the presence of catalytic copper(II) triflate, the conversion of the allylic hydroperoxide **2** of qinghao acid methyl ester **1** into the ketoaldehyde **5** proceeds via the simple enol **3** and aldol **4** (Scheme 1).[1] Under oxygen, the enol is oxygenated efficiently to provide the peroxyhemiacetal **6**; this key transformation has been used in the preparation of qinghaosu and derivatives.[2]



Scheme 1

A logical extension of this work is to examine the Cu(II)-catalysed oxygenation of enol ethers. While it has been demonstrated that singlet oxygenation of enol ethers in the presence of carbonyl compounds gives trioxanes,[3] less attention has been placed on the use of electron transfer agents and triplet oxygen to effect the oxygenation step. One prominent example involves formation of dioxetanes from adamantyl aryl enol ethers with oxygen and $(p\text{-}BrC_6H_4)3N^+SbCl_6^-$; reversible electron transfer from the enol ether provides a cation radical which undergoes oxygenation and electron transfer in a chain process involving the starting enol ether to give the dioxetane.[4,5] In our case, we have initially focussed on the alkyl enol ether **7**[6] which serves as a useful analogue of the enol **3**.

A 1:1 (*E*)/(*Z*) mixture of the enol ether **7** upon treatment with Cu(II) triflate (0.1 equiv) in anhydrous MeCN[7] at -20 °C under oxygen during less than 5 min gave the methoxyaldehyde **8** (*ca.* 40%) and ketoaldehyde **12** (<10%). Under these conditions, oxygenation was not observed. Inclusion of 1 equivalent of water resulted in very clean and rapid (< 5min) conversion of the enol ether **7** into two aldols **9** and **11** (40:60, 59%).[8,9] Again, no oxygenation was observed.



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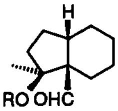
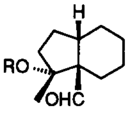
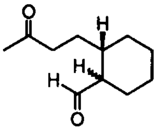


8 R = Me
9 R = H



10 R = Me
11 R = H



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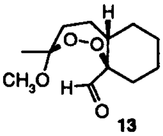

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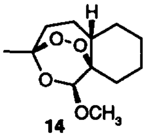

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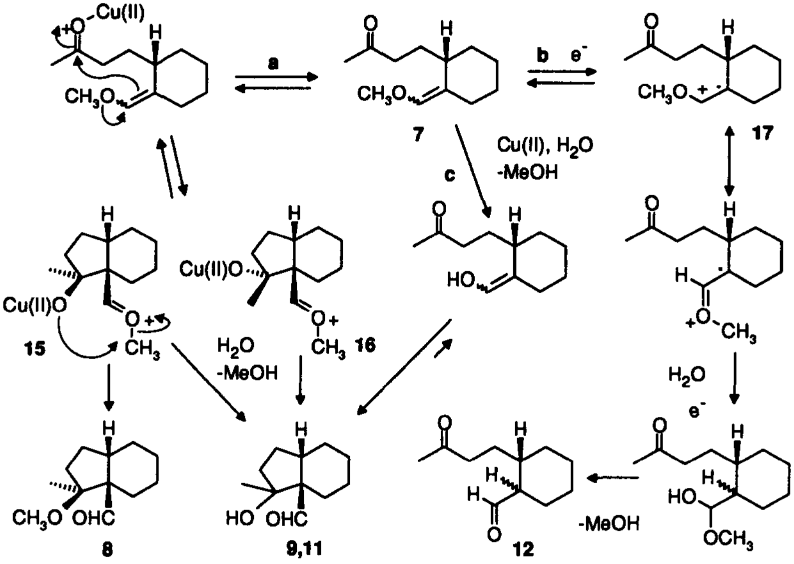
Notably, when the aldols, as generated above, were stirred in MeCN containing the copper catalyst with added MeOH (2.5% v/v) at 0-5 °C under oxygen, the aldols slowly disappeared, and after 24 h, the methoxyaldehyde **8** (12%) and a 93:7 mixture of the peracetal **13**[6] and the trioxane **14**[6,10] (47%, combined yield) were obtained after workup and chromatography. Next, each of the aldols were separated by HPLC and submitted to oxygenation. Thus, trans aldol **11** with Cu(II) triflate (0.1 equiv) in MeCN containing MeOH (2.5% v/v) at 0-5 °C under oxygen during 4 h was largely converted into the trans methoxyaldehyde **10** and the oxygenation products **13** and **14**, and small amounts of the cis methoxyaldehyde **8** and the cis aldol **9**. After a further 40 h the relative amounts of the methoxyaldehydes decreased to provide after workup and chromatography, the cis methoxyaldehyde **8** (4%), the trans methoxyaldehyde **10** (4%), the peracetal **13** (37%) and the trioxane **14** (2%). However, the cis aldol **9** under the same conditions reacted much more slowly and it took 72 h for most of the aldol to be consumed. Nevertheless, the reaction afforded the cis methoxyaldehyde **8** (5%), only a trace of the trans methoxyaldehyde **10**, the peracetal **13** (35%) and the trioxane **14** (8%) after 96 h.

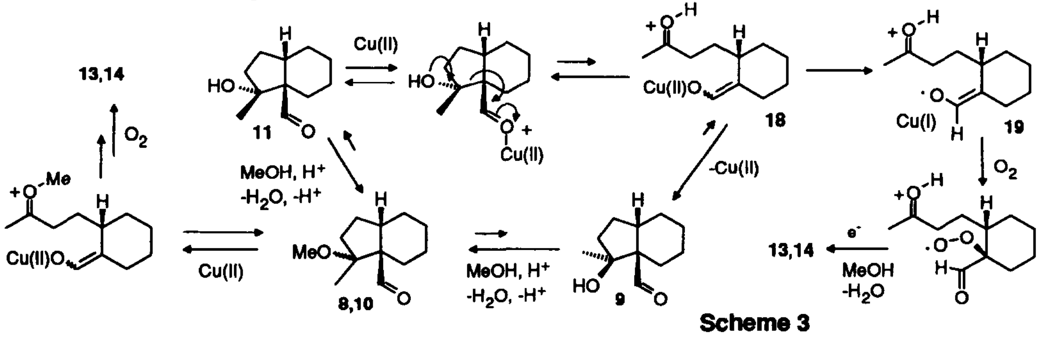
The results are rationalised as follows. Cu(II) triflate is a strong oxidant with $E^\circ > 1$ V[11] and while formation of the cation radical from the enol ether is a likely outcome,[12] reaction with oxygen clearly is not taking place. Possibly, this reaction is unable to compete with aldolisation.[13] In the present case, it is likely that Cu(II) triflate acts as a Lewis acid and catalyses aldolisation of the enol ether with the ketone carbonyl to provide methylated oxonium ions **15** and **16** (path a, Scheme 2) in which intramolecular methyl group transfer within **15** provides methoxyaldehyde **8**. Alternatively, hydrolysis of the oxonium ions **15** and **16** may compete to give the aldols **9** and **11**. Under low concentrations of water, cation radical (**17**) formation (path b) may compete with the aldolisation reactions and nucleophilic attack of water on the cation radical, followed by back electron transfer could account for the ketoaldehyde formation.[5] Stoichiometric amounts of water ensure that almost quantitative conversion to the aldols takes place either via hydrolysis of the enol ether **7** (path c) or the oxonium ions **15** and **16** and competes successfully with cation radical formation from the enol ether. This is indicated by the absence of the ketoaldehyde **12** under these conditions.

The next stage, conversion to the peracetal **13** and trioxane **14**, is without precedent in the literature[14] and is likely to proceed via a retroaldol reaction to yield a Cu(II) enolate **18** (Scheme 3). Electron transfer within the Cu(II) enolate leads to the Cu(I) enol radical **19** which then reacts with oxygen. The remarkable observation that the trans aldol **11** underwent more rapid oxygenation than the cis aldol **9** may be ascribed to a favourable antiperiplanar relationship of the groups in the trans aldol **11** participating in the retroaldolisation via a Grob-type cleavage.[15] We have noted previously that it is the trans isomer of the aldol **4** derived from qinghao acid methyl ester hydroperoxide **2** which undergoes facile cleavage in the presence of triflic acid to the ketoaldehyde **5**.[1] In the present case, when each of the cis and trans aldols **9** and **11** was treated with catalytic triflic acid (0.1 equiv) in MeCN under nitrogen the former remained unaffected, while the latter underwent almost complete conversion into the cis aldol **9** (82%) and the ketoaldehyde **12** (4%) after 2 min at -20 °C.



Scheme 2

In an attempt to promote the retroaldol reaction, and enhance the rates of oxygenation, triflic acid (0.01 equiv) was introduced after treating **11** with Cu(II) triflate (0.1 equiv) in the presence of MeOH at 0-5 °C. However, this led to steady formation of the methoxyaldehyde diastereomers **8** and **10** over *ca.* 1.5 h. Prolonging the reaction time to 66 h, caused the methoxyaldehydes to gradually diminish thereby providing the cis aldol **9** (8%), the trans aldol **11** (<1%), the peracetal **13** (35%), and the trioxane **14** (10%). In this case an additional set of equilibria involving methanolysis of the aldols and ring-opening arises. Provided that a steady concentration of enol or enolate is generated, in principle, all aldol and methoxyaldehyde diastereomers will be converted into oxygenation products although at different rates.



Scheme 3

In summary, it has been shown for the first time that acid-catalysed retroaldolisation in the presence of Cu(II) affords enols or Cu(II) enolates that are susceptible to oxygenation. This provides a new approach to α-hydroperoxy carbonyl compounds and derivatives. We are currently assessing the importance of these reactions.

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7. MeCN was distilled from P_2O_5 and stored under nitrogen over 4Å molecular sieves. All oxygenation experiments were carried out with 0.5-1 mmol of substrate in MeCN (0.06-0.08 M).
8. The same result was obtained with the separated (*E*)- or (*Z*)-isomers of **7**.
9. **9:** ^{1}H NMR (400 MHz) δ 0.94-1.02 (1H, m), 1.24 (3H, s, CH_3), 1.29-1.38 (1H, m), 1.39-1.54 (4H, m), 1.57 (1H, br s, OH), 1.65-1.72 (3H, m), 1.75-1.81 (1H, m), 1.94-2.00 (1H, m), 2.12-2.17 (1H, m), 2.60-2.65 (1H, m, H3a), 9.67 (1H, s, CHO). nOe's: Preirradiation at δ1.24 (CH_3) enhanced δ 1.64-1.74 (0.7%), 2.59-2.65 (H5, 1.6%), and 9.67 (CHO, 0.4%). Preirradiation at δ2.62 (H3a), enhanced δ 1.39-1.48 (6.8%). Preirradiation at δ 9.67 (CHO) enhanced δ 2.12-2.17 (2.4%), and δ 2.57-2.66 (H3a, 1.6%). **11:** ^{1}H NMR (400 MHz) δ 1.02-1.10 (2H, m), 1.27 (3H, s, CH_3), 1.30-1.41 (1H, m), 1.47-1.53 (2H, m), 1.78-1.77 (4H, m), 1.59-1.93 (1H, br s, OH), 1.86-2.02 (3H, m), 3.00-3.11 (1H, m, H3a), 9.79 (1H, s, CHO). Preirradiation at δ 1.27 enhanced δ 1.86-2.02 (0.9%), and 9.79 (0.1%). nOe's: Preirradiation at δ 3.06 enhanced δ 1.47-1.53 (2.2%), 1.57-1.61 (1.0%), and 1.78-2.02 (4.9%). Preirradiation at δ 9.79 enhanced δ 3.00-3.11 (2.4%), and 1.95-2.02 (3.4%).
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12. Schmittel, M. *Top. Curr. Chem.* **1994**, 184.
13. In certain intermolecular examples oxygenation to give trioxanes proceeds smoothly: Vonwiller, S. C.; Haynes, R. K. unpublished results.
14. A relevant case is the oxygenation with triplet oxygen of a potassium enolate generated by an oxyanionic Cope rearrangement: Paquette, L. A.; DeRussy, D. T.; Pegg, N. A. ; Taylor, R. T.; Zydowsky, T. M. *J. Org. Chem.* **1989**, *54*, 4576.
15. We are unaware of any study involving retroaldolisation which relates geometry to facility of cleavage.

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