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Rate Enhancement in the Wacker Oxidation of Hydroxy-α,β-unsaturated Esters: A Fast Neutral Method for the Preparation of Masked β-Ketoesters

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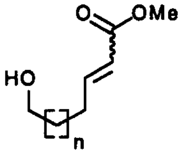
Key Words : **Wacker oxidation; intramolecular; hydroxyalkenoate eaters; neutral.**

Abstract : **Wacker oxidation of 6- or 7-hydroxyalkenoate esters is a mild one step means of generating both simple and highly functionalized protected β-ketoesters in high yield, under essentially neutral conditions.**

The industrial oxidation of ethylene by palladium@) catalysts known as the Wacker oxidation has been developed into an efficient method of oxidizing terminal alkenes to methyl ketones in the organic laboratory.[1] However, the oxidation of internal alkenes is a more difficult problem. The oxidation of such alkenes is complicated by the question of regiochemistry. Additionally, oxidation of internal alkenes using the standard **palladium(II)** chloride / **copper(II)** chloride / oxygen catalyst system is dramatically slower than for terminal alkenes. The regiochemistry of these oxidations may be controlled by electron withdrawing substituents, thus **α,β-unsaturated** esters are specifically oxidized at the **β-carbon,** however, the rate of this reaction is very slow.[2] Oxidation of **α,β-unsaturated** esters proceeds at a faster rate at 500C in aqueous acetic acid employing sodium tetrachloropalladate **(20Mol%)** as the catalyst and t-butyl hydroperoxide or hydrogen peroxide as the **reoxidant.**[3] Although the reported yields were moderate, the substrates lacked additional functionality. Hosokawa has shown that Wacker oxidation of vinyl ketones and acrylate esters in the presence of **1,2-** or **1,3-diols** gives the analogous cyclic **acetals,**[4] however, the oxidation of more substituted esters and ketones was very slow.



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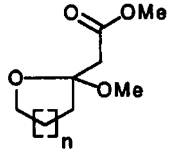
n=I 6



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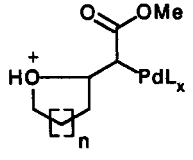


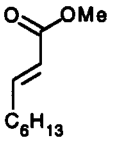
n = 2 3

In connection with the synthesis of venturicidin5 we were interested in developing a mild method under neutral conditions for the conversion of c&unsaturated esters to protected **β-ketoesters.** We thought that oxidation of alkene **1,** to give protected **β-ketoester 2,** by way of intramolecular nucleophilic addition to generate alkyl palladium species **3** would be significantly enhanced with respect to the intermolecular variant. This concept has not previously been employed to overcome the unreactive nature of internal alkenes. Under Hosokawa's conditions, alkene **1** was slowly oxidized to give **2** as one component (44%) of a complex mixture. However, using a mixture of **CuCl(3eq.)** and **$CuCl_2$(3eq.)** as the reoxidant, in the presence of **LiCl(6eq.)** gave the desired product in excellent yield (89%). It was found that use of either less reoxidant, or omission of **LiCl** was detrimental to the yield of **2.** In extending this result to other alkenes we have found the requirement for **LiCl** is not general.

We have extended this result to the oxidation of an interesting range of hydroxy-a&unsaturated esters (Table **1).**[6] Of note is the tremendous rate enhancement due to the presence of the hydroxyl unit. Oxidation of methyl **2-nonenoate 4** was run as a comparative standard. Under the optimum conditions (either with or without **LiCl),** oxidation of **4** over a 14 day period gave a poor **yield(20%)** of cyclic **acetal 5,** along with significant recovery of the substrate (50%). By contrast, the hydroxyalkenes were cleanly consumed within 3 days. Formation of the **5-membered** semicyclic acetals **7, 13, 15,** was much faster than that of the corresponding **6-membered** species **2, 9, 11** (Entry 2 **vs** 3, and 4 and 5 vs 6). Oxidation of primary alcohols, **1** or **6,** appears to be slightly less facile than that of secondary alcohols (Entry 2 vs 4 and 5, and 3 vs 6). This result may be a consequence of the solution conformations of these species. Of interest was the oxidation of arabinose derivative **14.** Under acidic conditions this species would be stereochemically labile, resulting in racemization of the **C_4-center.** However, oxidation of **14** resulted in less than 5% of epimerized species. Oxidation of **14** gave a 3: 1 mixture of **15** and **17** in good yield. Of the two products which may result from **14, β-furanoside 15** is predicted7 to be of lower energy than a-furanoside **16,** whilst enolether **17** is intermediate in stability. Confirmation of the structure of **17** was attained by conversion to **15** upon treatment with catalytic TSA in dry **MeOH.** This clearly demonstrates the mild non-acidic nature of our oxidation conditions. Studies are presently underway to explore the potential of this process in the elaboration of simple carbohydrates.8

In the presence of **LiCl** all of these oxidations proceeded at a slower rate, but eventually provided complete oxidation of the substrate. Whereas, in the absence of **LiCl,** those oxidations which proceeded over a number of days often terminated prior to complete consumption of the alkene.

Indeed, the presence of Cl$^-$ has been correlated with a retardation of the rate of oxidation in similar systems,[9] presumably through chloride complexation of the active catalyst. We suggest that this complexation may also reduce the rate at which the active catalyst under goes irreversible destruction.



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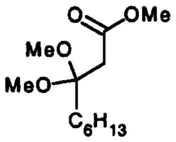

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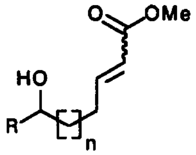
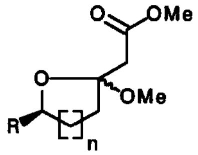
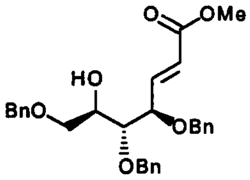


R = CH$_2$Ph, n = 2 8
R = C$_7$H$_{15}$, n = 2 10
R = C$_5$H$_{11}$, n = 1 12



R = CH$_2$Ph, n = 2 9
R = C$_7$H$_{15}$, n = 2 11
R = C$_5$H$_{11}$, n = 1 13



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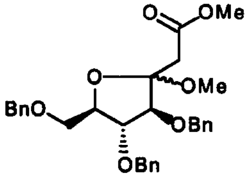
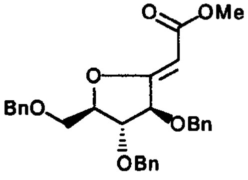


β-OMe 15
a-OMe 16

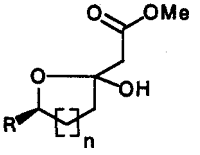


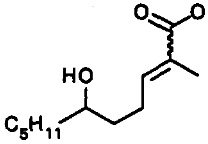
17

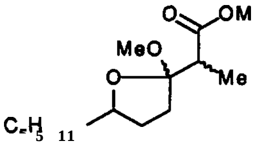
Entry	Substrate	Product	Time(hr)	Yield(%)
1	4	5	14 days	20
2	1	2	60*	87*
3	6	7	22	62
4	8	9	44*	61
5	10	11	48*(24)	79*(72)
6	12	13	4	87
7	14	15 + 17	8	43 + 17

Table 1 (* indicates the oxidation was performed in the presence of LiCl(6eq.))

Trisubstituted alkenes usually under go very slow Wacker oxidation, however, oxidation of trisubstituted alkene 20 is complete within 76hr to give acetal 21(54%) as a inseparable mixture of diastereomers. Such highly substituted acetals are not as readily available employing other traditional techniques. This result clearly shows the advantage of the intramolecular Wacker oxidation. Alternatively, oxidation of 1 and 12 in aqueous THF gave equilibrating mixtures of the hemiacetals 18 and 19 and the corresponding β-ketoesters in lower yields (38% and 31% respectively). The lower yields may be a result of the lower solubility of the catalyst system in aqueous THF.







n = 2 R = H 18 20 21

n = 1 R = C_5H_{11} 19

It may be argued that chelation of the hydroxyl oxygen to the palladium and subsequent intramolecular delivery of the catalyst to the alkene is the cause of the rate enhancement observed for these alkenes. However, oxygen ligands bind weakly to such palladium catalysts.[10] Rather, this result may be a consequence of the high rate enhancements observed in intramolecular reactions.11 Nucleophilic intramolecular reactions may result in high rate enhancements compared to the inter-molecular variants. Our results indicate an effective molarity of the hydroxyl group of 10^2-10^3. This suggests that addition to the palladium alkene x-complex is the rate limiting step not the formation of the x-complex.

In summary we have shown that the Wacker oxidation may be employed in the fast and clean one step preparation of masked β-ketoester under almost neutral reaction conditions. In addition we have identified a key factor in the Wacker oxidation of internal alkenes which may be valuable in the future utility of this reaction in a synthetic sense.

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