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Pyridinium Oxidations of Benzyl Alcohol Under Microwave-Assisted Retro-Ene Conditions

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ABSTRACT

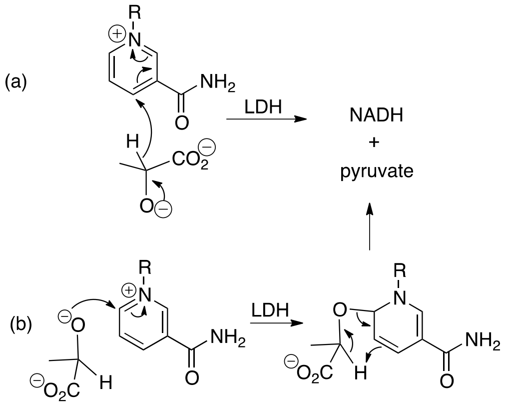
Benzyl alcohol is oxidized to benzaldehyde when heated in sulfolane in the presence of N-benzylnicotinamide and N-benzylpyridinium salts. The oxidation is accelerated in the presence microwaves. Oxidations with related pyridiniums suggest that these oxidations could occur via retro-ene reactions.

Oxidation; Pyridinium; NAD+, Benzyl Alcohol

Pyridinium salts are known to oxidize alcohols to aldehydes or ketones. The most notable pyridiniums to do so are the enzymatic cofactors NAD$^+$ and NADP$^+$. Various synthetic models of these cofactors have been made and are known to oxidize alcohols non-enzymatically with low to moderate yields.[1] These synthetic analogs are inevitably decorated with electron withdrawing groups, since both biological and synthetic pyridiniums have long been thought to carry out these oxidations by accepting a hydride from deprotonated alcohols.[2]

However, recent model and enzyme studies on NAD(P)H have found ene reaction intermediates in biological reductions mediated by dihydropyridines.[3] These findings suggest that NAD(P)H reduces carbonyl groups not by a hydride mechanism, but rather an ene reaction mechanism.

The ene reaction (mechanistically similar to the Diels-Alder) occurs when an allylic system (ene), transfers a hydrogen atom to an alkene (enophile).[4] Various mechanisms have been proposed, the most common ones are shown in scheme 1.[5] Both ene and enophile may contain heteroatoms.[6]



Scheme 1. Ene Reaction Mechanisms

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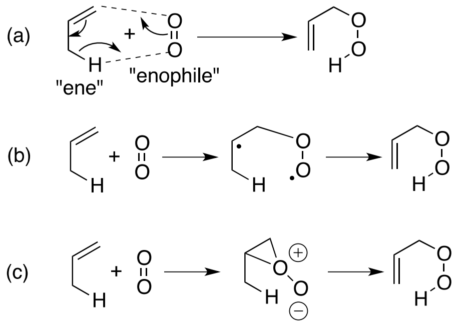
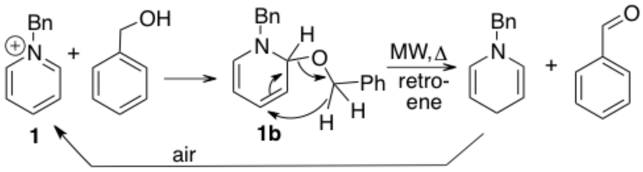


If NADH reduces via the ene reaction, it is likely that oxidation of alcohols by NAD$^+$ occurs through a retro-ene reaction (similar to the retro-Diels-Alder). The retro-ene reaction is the fragmentation of a six-atom system into an ene and enophile.[7] This reaction usually requires high temperature but under certain conditions can occur at or near ambient temperature.[8]

An example of an enzymatic oxidation of alcohols by NAD$^+$ is the oxidation of lactate to pyruvate by lactate dehydrogenase (LDH).[9] The traditional mechanism involving hydride transfer to the pyridinium ring is shown in scheme 2a. An aternate mechanism involving addition of an alcohol to the pyridinium followed by a retro-ene step (shown in 2b) was originally proposed by Hamilton.[3b,10]

Scheme 2. LDH Mechanisms



Scheme 4. Oxidation Mechanism

With these new mechanistic insights in mind we set out to test the ability of synthetic pyridiniums to carry out oxidations under retro-ene reaction conditions instead of hydride transfer conditions. Retro-ene reactions of this type generally require high temperatures and would not necessarily require deprotonation of the alcohol, as in a hydride transfer, or the presence of electron withdrawing groups, as in an electron transfer mechanism.

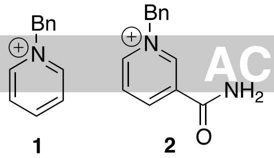
Synthetic NAD$^+$ analogs **1** and **2** were made by reacting pyridine or nicotinamide with benzyl bromide.[11] Both **1** and **2** oxidize benzyl alcohol to benzaldehyde upon heating at 190 °C for five minutes, in a sealed container, in a microwave reactor with sulfolane solvent (scheme 3). Without microwave acceleration, the reaction requires 1 – 2 hours of heating. The amide substituent of **2** appears to slow the reaction relative to unsubstituted pyridinium **1**. To the best of our knowledge, oxidation via pyridinium **1** is the first example of the oxidation of an alcohol by a pyridinium without additional electron withdrawing groups on the pyridinium ring. These reactions are also the first example of microwave acceleration in alcohol oxidations by pyrdiniums.

Scheme 3. Oxidation Reactions

Control reactions showed that a small amount of benzaldehyde forms when benzyl alcohol is heated in sulfolane at 190 °C without **1** or **2**, but this reaction occurred at a much slower rate, forming orders of magnitude less aldehyde. No benzaldehyde is formed when **1** is used without alcohol under reaction conditions, although **1** does slowly decompose.

Sulfolane is an ideal solvent for this reaction. It also has a high boiling point and excellent thermal stability. Its very high dipole moment dissolves both pyridinium and reactant. And it is excellent for nucleophilic additions to aromatic rings because it doesn't complex with nucleophiles. SNAr reactions proceed very well in sulfolane.[12]

If the reaction occurs through a retro-ene mechanism, the first step would be addition of benzyl alcohol to the 2, 4, or 6 position of the pyridinium. A thermal retro-ene could then occur forming an aldehyde and dihydropyridine (see scheme 4). Dihydropyridines are not air stable, especially at elevated temperature, and would re-oxidize to pyridiniums under our conditions.[1a,1g]



1 2

We have attempted to observe potential intermediate **1b** (see scheme 4) but have been unsuccessful. At elevated temperatures **1b** would have a very short lifetime. At room temperature, equilibrium would largely favor the aromatic starting material. Attempts to observe **1b** through ESI-MS or trap **1b** through addition of reactive Diels-Alder dienophiles have so far been unsuccessful.

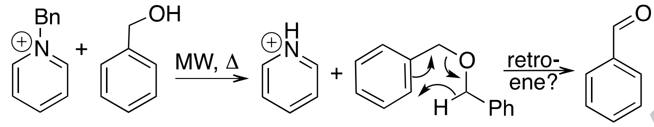
However, nucleophiles are known to add to either the 2/6- or 4-positions of pyridinium rings.[13] Addition to the 2/6-position appears to be more likely because only softer nucleophiles add predominantly to the 4-position.[13] Nucleophiles are also known to do substitutions at the benzyl position and deprotonate relatively acidic pyridinium *ortho* hydrogens.[13,14]

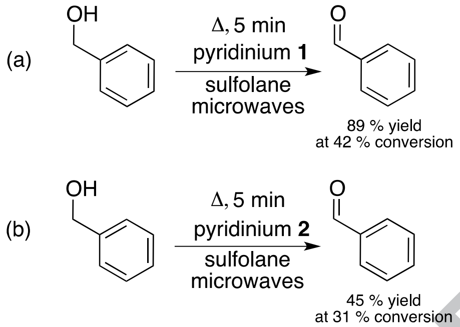
An alcohol adduct has been observed, by UV spectroscopy, to add to a pyridinium at the 2-position. This alcohol was tethered to the pyridinium nitrogen by a three-carbon bridge. Conformationally, this alcohol is unable to undergo a retro-ene with the 4-position of the ring.[1c]

Additional tests, suggested by reviewers, have revealed a minor competing mechanism likely contributing to some aldehyde formation and catalyst decomposition. When 4-nitrobenzyl alcohol is used in place of benzyl alcohol, a mixture of 4-nitrobenzaldehyde (major) and benzaldehyde (minor) is formed. This suggests that the alcohol starting material can displace the benzyl group of the pyridinium to form an unsymmetrical benzyl ether capable of forming both aldehydes.[15] Indeed, small amounts of dibenzyl ether are seen in typical reaction NMRs.

Scheme 5. Alternate mechanism

To test this alternate mechanism (through benzyl ethers), we used dibenzyl ether in place of benzyl alcohol in typical reaction conditions and observed formation of benzaldehyde, but only when **1** is present. When **1** is not present, the ether doesn't form aldehyde. We also followed loss of starting material and formation of product(s) by NMR during a typical reaction with between benzyl alcohol and **1**. After about three minutes the amount of catalyst **1** had decreased from 0.4 mmol to 0.3 mmol. At the same time 0.03 mmol of ether was present in the solution, but 0.4 mmol of aldehyde had already formed. If only 25% of the 1 had decomposed, and aldehyde was only formed via that decomposition, then far less aldehyde should have been present.



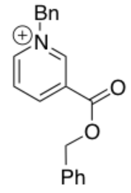


We also made benzyl 4-nitrobenzyl ether and reacted it with **1** under typical conditions. It forms a small amount of both 4-nitrobenzaldehyde and benzaldehyde (about 1:1), but also forms numerous other products that are not observed when 4-nitrobenzyl alcohol reacts with **1**.

While it may not be possible to isolate **1b** and test its reactivity under thermal conditions, it is possible to make similar compounds to test the ability of pyridiniums to undergo retro-ene type reactions. For example, we synthesized two additional pyridiniums, **3** and **4** (which is a new compound).[16] Both of these pyridiniums have the potential to form benzaldehyde through a retro-ene mechanism (shown in scheme 6). Heating **3** or **4** in sulfolane at 190 °C for five minutes in a microwave reactor produced benzaldehyde in about 25% yield (81% and 64% conversions respectively) and pyridinium decomposition products.

Scheme 6. MW-assisted pyrolysis of **4**

In conclusion, compounds **1** and **2** effectively oxidize benzyl alcohol to benzaldehyde when heated in sulfolane at 190 °C for five minutes in a microwave reactor. The thermal reaction conditions are consistent with a retro-ene mechanism. Using a pyridinium without electron withdrawing groups (such as **1**) and microwave enhancement are both new to this field of research. The polar, aprotic, and high boiling sulfolane solvent is ideal for the reaction. Forming benzaldehyde upon pyrolysis of **3** and **4** also suggests a retro-ene reaction is possible for pyridiniums. These findings are consistent with recent studies suggesting that NAD(P)H reacts through an ene mechanism.[3] Further research is underway to study stabilization of the catalyst and prevention of side reactions, such as formation of benzyl ethers.



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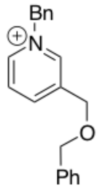

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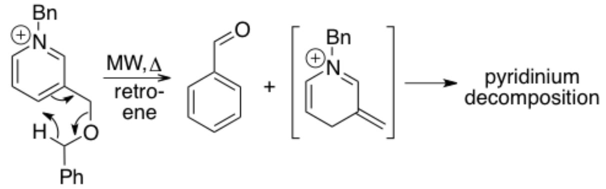

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Supplementary Material

Supporting Information is available and includes the syntheses of compounds 1-4 and an example of the thermal microwave reactions.

Highlights

- Benzyl alcohol is oxidized by a pyridinium lacking an electron-withdrawing group.
- The reaction is microwave-assisted.
- A Retro-Ene type mechanism is proposed.

Graphical Abstract

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