

## Palladium-Catalyzed Oxidation of *N,N*-Diethyl-2,7-octadienylamine to *N,N*-Diethyl-6-oxo-2-octenylamine

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The terminal double bond of *N,N*-diethyl-2,7-octadienylamine is selectively oxidized by *p*-benzoquinone or hydrogen peroxide in dilute hydrogen chloride in the presence of a catalytic amount of sodium tetrachloropalladate. Although the same product is formed using both oxidants, the reactions proceed *via* different mechanisms.

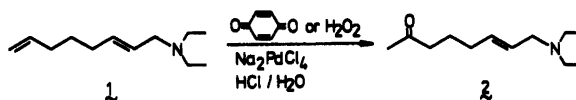
Wacker-type oxidation of terminal olefins to methyl ketones using palladium chloride and an oxidant, usually  $\text{Cu}^{2+}/\text{O}_2$  or *p*-benzoquinone, is a well-known reaction,<sup>1,2</sup> which has important synthetic applications.<sup>3</sup> The oxidation proceeds under mild conditions and can be performed in the presence of various functional groups, such as carboxylic acid, ester, aldehyde, alcohol, chloride and bromide. Recently, Mimoun has demonstrated that hydrogen peroxide and organic hydroperoxides are also efficient oxidants for terminal olefins when palladium(II) reagents are used as catalysts.<sup>4,5</sup>

Various 2,7-octadienyl derivatives are conveniently prepared by palladium-catalyzed telomerization of butadiene and nucleophiles such as acetate,<sup>6,7</sup> malonates,<sup>8</sup> amines<sup>6,7,9–12</sup> and alcohols.<sup>6,13</sup> Oxidation of the terminal double bond of such telomers affords methyl ketones which have been shown to be useful synthons in the syntheses of various natural products.<sup>3</sup> We have investigated palladium-catalyzed oxidations of *N,N*-dialkyl-2,7-octadienylamines and have discovered conditions which permit the presence of an amine function in the substrate.

### RESULTS AND DISCUSSION

*The reaction.* Compound *1* is unchanged after heating in dimethylformamide (DMF) under normal Wacker-type conditions.<sup>14</sup> In dilute hydrogen chloride (0.6–2 M), however, *1* is selectively oxidized to the aminoketone *2* in high yields within 3 h at 60 °C using *p*-benzoquinone and a catalytic amount (20 %) of sodium tetrachloropalladate.

Oxidation of *1* to *2* also occurs when *p*-benzoquinone is replaced by hydrogen peroxide, with the advantage that water is formed as the by-product. Hydrogen peroxide is, however decomposed with oxygen evolution by Pd(II) and this decomposition is a serious side reaction in cases where this oxidant is used.<sup>4</sup> Consequently, an excess ( $\geq 3$  eq.) of hydrogen peroxide has to be used in order to allow the reactions to go to completion.

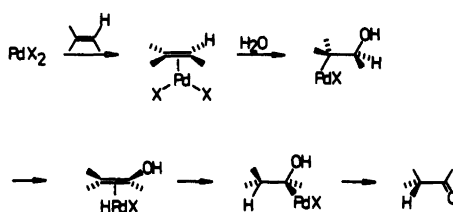


Strongly coordinating groups such as amines are known to inhibit the Wacker reaction.<sup>15</sup> At low pH, however, protonation of the amino groups prevents their coordination to palladium and the oxidation proceeds smoothly. The aminoketone 2 slowly polymerizes on standing, but this decomposition is also inhibited by protonation at nitrogen.

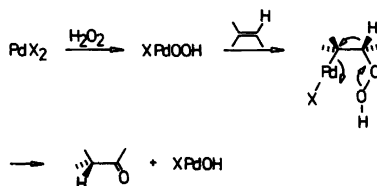
When the oxidations of 1 under various conditions were followed by GLC or by <sup>1</sup>H NMR (using DC1/D<sub>2</sub>O) it became apparent that the yield of compound 2 and also its rate of formation and decomposition is indeed strongly dependent on the amounts of acid and H<sub>2</sub>O<sub>2</sub> in the reaction mixture. The highest yield of 2 (82 % crude product) was obtained using 3 eq. of acid (based on the amine) and 3 eq. of H<sub>2</sub>O<sub>2</sub>. Higher and lower amounts of acid resulted in lower yields and a more rapid decomposition of the product, whereas a larger excess of H<sub>2</sub>O<sub>2</sub> resulted in a higher reaction rate, but did not influence the yield or the rate of decomposition.

Venanzi has recently demonstrated that aminoalkenes are oxidized in acidic medium using the system Pd<sup>2+</sup>/Cu<sup>2+</sup>/O<sub>2</sub>.<sup>16</sup> Under these conditions, however, extensive palladium-catalyzed double bond isomerization takes place. Thus, from *N,N*-dimethyl-5-hexenylamine, a 65:35 mixture of *N,N*-dimethyl-5-oxo-hexylamine and *N,N*-dimethyl-4-oxo-hexylamine was obtained.

**Mechanism.** The mechanism of the Wacker reaction has been extensively studied.<sup>15</sup> The key step appears to be nucleophilic attack by water or hydroxide on the coordinated olefin to give a  $\sigma$ -bonded  $\beta$ -hydroxypalladium species (Scheme 1). The hydroxypalladation has been shown, at least under certain conditions, to be a *trans* process.<sup>17,18</sup> By contrast, a palladium-hydroperoxide species, obtained by reaction of H<sub>2</sub>O<sub>2</sub> with Pd(II) compounds, adds to olefins in a *cis* manner (Scheme 2).<sup>19,20</sup> Decomposition with  $\beta$ -hydride migration and O—O bond rupture of the peroxy-palladated olefin eventually affords the ketone. Usually anhydrous solvents such as acetic acid or *t*-butanol have been used in the latter reactions, but even in the presence of some water, H<sub>2</sub>O<sub>2</sub> has been shown to be the oxygen source.<sup>5</sup>



Scheme 1.



Scheme 2.

In order to determine whether water or hydrogen peroxide is the attacking species in the oxidation of *N,N*-diethyl-2,7-octadienylamine by hydrogen peroxide, the reaction was performed in water enriched with  $^{18}\text{O}$  (99 %) using unlabelled  $\text{H}_2\text{O}_2$ . The  $^{18}\text{O}:^{16}\text{O}$  ratio in the product was determined *versus* time by mass spectrometry (MS) (This procedure has also been used by H. Mimoun et al.<sup>5</sup>) After 5 min reaction at 60 °C no product containing  $^{18}\text{O}$  could be detected. As the reaction proceeded the  $^{18}\text{O}:^{16}\text{O}$  ratio, due to hydrate formation, approached an equilibrium value corresponding to the amounts of  $^{18}\text{O}$  and  $^{16}\text{O}$  present in the solution. This result clearly shows, that even in cases where water is used as solvent, the source of oxygen is  $\text{H}_2\text{O}_2$ .

## EXPERIMENTAL

*N,N*-Diethyl-2,7-octadienylamine hydrochloride was prepared by reaction of *1*<sup>21</sup> with gaseous HCl (obtained by the addition of  $\text{H}_2\text{SO}_4$  to NaCl and dried with conc.  $\text{H}_2\text{SO}_4$ ) in diethyl ether.  $\text{Na}_2\text{PdCl}_4$  was prepared from  $\text{PdCl}_2$  and NaCl in methanol.  $\text{H}_2\text{O}_2$  was used as a 35 % solution in water.  $\text{H}_2^{18}\text{O}$  (99 %) was purchased from Stohler Isotope Chemicals.

$^1\text{H}$  NMR spectra were recorded on a JOEL JNM-PMX instrument at 60 MHz and on a Bruker WP 200 FT instrument at 200 MHz ( $\text{CDCl}_3$  as solvent and TMS as internal standard); infrared spectra on a Perkin Elmer 257 spectrometer and mass spectra on a Finnigan 4021 GLC-MS instrument at 70 eV. Gas chromatography was performed on a Pye GCD instrument using a 1.2 m $\times$ 2 mm column of 5 % SE 30 on Chromosorb W.

*Oxidation of 1.* To the amine *1* (360 mg, 2 mmol), dissolved in 0.5 M HCl (12 ml) was added  $\text{Na}_2\text{PdCl}_4$  (118 mg, 0.4 mmol) at 60 °C and the mixture was stirred for 15 min.  $\text{H}_2\text{O}_2$  (406  $\mu\text{l}$ , ca. 6 mmol) was added in two portions during 15 min and the mixture was stirred at 60 °C. The reaction was followed by GLC by taking aliquots (100  $\mu\text{l}$ ) of the reaction mixture. The samples were made alkaline and extracted with 250  $\mu\text{l}$  of an ethereal solution of hexadecane (0.02 mmol/ml), which was used as an internal standard. During the reaction the green mixture gradually turned into a brownish red solution. After 0.5 h reaction, 2 M NaOH (5 ml) was added in three portions and the aqueous phase was extracted with  $\text{CH}_2\text{Cl}_2$  (20 ml) after each addition. The combined organic phases were dried ( $\text{MgSO}_4$ ) and the solvent evaporated to yield crude *2* (323 mg, 82 %). Oxidations with *p*-benzoquinone were performed in the same way using 1 mmol of *p*-benzoquinone (108 mg), which was added in one portion. Attempts to purify *2* by flash chromatography or distillation gave a less pure product, probably due to dimerization and oligomerization of the product.  $^1\text{H}$  NMR (200 MHz):  $\delta$  1.03 (t, 6 H,  $J=7.2$  Hz), 1.66 (quint., 2 H,  $J=7.3$  Hz), 1.95–2.1 (m, 2 H), 2.13 (s, 3 H), 2.43 (t, 2 H,  $J=7.3$  Hz), 2.52 (quart., 4 H,  $J=7.2$  Hz), 3.05 (d, 2 H,  $J=5.0$ ), 5.5 (m, 2 H). IR ( $\text{CCl}_4$ ): 1715  $\text{cm}^{-1}$ . MS (70 eV)  $m/z$  (rel. intensity): 197 (2), 182 (14), 125 (43), 112 (32), 86 (100).

*Oxidation of 1 in  $\text{H}_2^{18}\text{O}$ .* To the hydrochloride of *1* (0.167 mmol), dissolved in  $\text{H}_2^{18}\text{O}$  (250  $\mu\text{l}$ ) was added  $\text{Na}_2\text{PdCl}_4$  (9.8 mg, 0.033 mmol). The mixture was heated at 60 °C for 10 min and  $\text{H}_2\text{O}_2$  (11  $\mu\text{l}$ , ca. 0.17 mmol) was added. Samples of 50  $\mu\text{l}$  were withdrawn, 5  $\mu\text{l}$  of 1.0 M NaOH (ca. 0.15 eq. based on the amine) was added, the water phase extracted with 250  $\mu\text{l}$  of diethyl ether and the GLC/MS recorded. The  $^{18}\text{O}:^{16}\text{O}$  ratio in the product was determined from the  $m/z$  199:197 and 184:182 ratios.

*Acknowledgements.* The authors thank Mr. Mikael Lindström for recording the mass spectra. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged.

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Received November 5, 1984.