Conjugate Addition of Diphenylphosphine.
Synthetic and Mechanistic Implications

An Honors Thesis (ID 499)

by

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Synthetic and Mechanistic Implications

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Introduction

Diphenylphosphine has long been known to add to electron-deficient alkenes by conjugate addition. For example, the addition of diphenylphosphine and acrylonitrile yields 3-diphenylphosphinopropanonitrile. The reaction is carried out in acetonitrile with a small amount of aqueous hydroxide as catalyst. The product is extracted and distilled. The mechanism presumably involves addition of diphenylphosphide, formed in small amounts, followed by protonation. No systematic study of variations in conditions or substrates has been reported, nor has a study of the mechanism of the reaction been published.

Results and Discussion

Diphenylphosphine was added to a variety of electron-deficient alkenes. Some of the reactions proceeded in good yield without hydroxide. Others required the addition of some tetraethylammonium
Acrylonitrile + PH → PHC≡N

Methyl vinyl ketone

Acrolein + PH → PH=C=O

Methacrolein

Ethyl methacrylate + PH → PHOC=O-CH₂CH₃

Methyl methacrylate + PH → PHOC=O-CH₃
hydroxide. A third group of alkenes were so reactive that they exploded the solvent out of the container unless special precautions using slow addition of dilute solutions were taken.

\[
\begin{align*}
\text{Ph} + \text{O-CH}_3 & \rightarrow \text{P} - \text{O-CH}_3 \\
\text{Methyl acrylate} \\
\text{Ph} + \text{O-CH}_2\text{CH}_3 & \rightarrow \text{P} - \text{O-CH}_2\text{CH}_3 \\
\text{Ethyl crotonate} \\
\text{Ph} + \text{O-CH}_2\text{CH}_3 & \rightarrow \text{P} - \text{O-CH}_3 \\
\text{Ethyl cinnamate}
\end{align*}
\]

Yields as indicated by NMR were above 90 per cent in most cases. It was important to run the reactions under argon in order to prevent the formation of phosphine oxides. Furthermore, the reactions were run on a small scale because diphenylphosphine is both noxious and expensive. Preliminary reactions were done on the NMR tube scale (10^{-6} molar reactants and 0.8 ml solvent). Scale-up reactions were carried out with three milliliters of diphenylphosphine, an excess of the alkene, and ten milliliters of solvent. Deuterochloroform was a solvent of choice in those reactions not requiring a base catalyst. When base was used, a switch to acetonitrile or dimethylsulfoxide was necessary. Most of
the successful reactions were exothermic at the beginning and an immediate color change (from colorless to yellow through brown) was frequently noted.

Reactions were easily followed with the proton NMR spectra. In the region 4-7 $\delta$, peaks due to the $sp^2$ carbon-bound hydrogens and the hydrogen bound to the phosphine were observed to decrease as peaks in the region 1.5-4 $\delta$ due to products were increasing in intensity.

**Figure 1. PROTON NMR CHEMICAL SHIFTS FOR DPP ADDUCTS**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$C_\alpha$</th>
<th>$C_\beta$</th>
<th>$C_\gamma$</th>
<th>$\alpha$-methyl</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acrolein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrylonitrile</td>
<td>1.8</td>
<td>2.3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ethyl cinnamate</td>
<td>2.8</td>
<td>4.12</td>
<td></td>
<td>Ethyl 3.83, 0.93</td>
<td></td>
</tr>
<tr>
<td>Ethyl crotonate</td>
<td>2.60-2.05</td>
<td>2.86</td>
<td>1.08</td>
<td>Ethyl 4.09, 1.21</td>
<td></td>
</tr>
<tr>
<td>Ethyl methacrylate</td>
<td>2.20-2.04</td>
<td>2.4-2.6</td>
<td>1.29</td>
<td>Ethyl 4.06, 1.21</td>
<td></td>
</tr>
<tr>
<td>Methacrolein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Methylacrylate</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Methyl methacrylate</td>
<td>2.56-2.17</td>
<td>2.61</td>
<td>1.34</td>
<td>Methyl 3.30</td>
<td></td>
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<tr>
<td>Methyl vinyl ketone</td>
<td>2.2-2.5</td>
<td>2.4-2.6</td>
<td></td>
<td>Methyl 2.06</td>
<td></td>
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### Figure 2. 13-C NMR CHEMICAL SHIFTS FOR DPP ADDUCTS

<table>
<thead>
<tr>
<th>Compound</th>
<th>$C_{\alpha}$</th>
<th>$C_{\beta}$</th>
<th>$C_{\gamma}$</th>
<th>$\alpha$-methyl</th>
<th>$C=O$</th>
<th>Other</th>
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<td>Acrylonitrile</td>
<td>14.28</td>
<td>24.40</td>
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<td>Ethyl cinnamate</td>
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<tr>
<td>Ethyl crotonate</td>
<td>26.6</td>
<td>37.8</td>
<td>16.5</td>
<td>171.9</td>
<td>Ethyl 60.0, 14.0</td>
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<tr>
<td>Ethyl methacrylate</td>
<td>33.0</td>
<td>37.8</td>
<td>19.0</td>
<td>176.7</td>
<td>Ethyl 60.1, 14.4</td>
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<tr>
<td>Methacrolein</td>
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<tr>
<td>Methylacrylate</td>
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<td>30.77</td>
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<td>172</td>
<td>Methyl 52.0</td>
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<tr>
<td>Methyl methacrylate</td>
<td>32.97</td>
<td>37.35</td>
<td>18.77</td>
<td>176</td>
<td>Methyl 51.98</td>
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<tr>
<td>Methyl vinyl ketone</td>
<td>21.57</td>
<td>40.04</td>
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<td>208</td>
<td>Methyl 30.0</td>
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### Experimental Section

Infrared spectra were recorded on a Nicolet 5ZDX FT-IR Spectrometer. 1-H and 13-C Nuclear Magnetic Resonance (NMR) spectra were measured with a Varian Gemini-200 Spectrometer and chemical shifts ($\delta$) are reported in parts per million downfield from Me$_4$Si. 31-P NMR spectra were measured with a Varian FT-80A Spectrometer.

Small scale synthesis without base. 1.00 mM of diphenylphosphine was added at once to 1.00 mM of acrylonitrile contained in 0.80 ml of CDCl$_3$. The reaction was allowed to proceed to completion while being monitored by loss of alkene proton NMR
signal. The NMR spectrum no longer changed after a period of 24 hours. The product was characterized by NMR (Table 1).

Methylacrylate (1.00 mM) was reacted with diphenylphosphine in the same manner. Again, the reaction was observed to be complete after 24 hours. Signals in the reactant region of the proton NMR (4-7 δ) were observed to disappear as a new product signal appeared at δ 2.6.

Methyl vinyl ketone was also reacted with diphenylphosphine on the NMR tube scale (1.00 mM). Vinyl peaks at δ 5.8-6.2 disappeared and new peaks at δ 1.8-2.6 were observed.

Methyl methacrylate was reacted on the 1.00 mM scale as well. Peaks in the proton NMR region δ 5.5 and 6.1 were reduced with the formation of a new peak at δ 3.6.

Ethyl methacrylate (62 μL) was reacted with 87 μL of Diphenylphosphine on a 0.50 mM scale. A volume of 0.80 ml of DMSO was used as solvent. The reaction proceeded in the same manner as the methyl methacrylate reaction with vinyl peaks and P-H peaks disappearing and new peaks appearing in the aliphatic region.

When diphenylphosphine was reacted with acrolein in the same manner, a violent exothermic reaction occurred. Immediately after the alkene was added, a solid precipitate was formed. The reaction was done in CDCl₃ and in deuteroacetone. The alkene peaks and the aldehyde peak disappeared, but the phosphine peaks (δ 4.7 & 5.8) did not. Apparently, the acrolein polymerized and formed an insoluble solid.

**Small scale with base in DMSO-d₆.** Ethyl cinnamate did not react with diphenylphosphine in CDCl₃. However, when reacted with base in a more suitable solvent (DMSO), the desired product was formed in
great yield. The base used was tetraethylammonium hydroxide. 0.23 mM of DPP and ethyl cinnamate were reacted in the presence of 10 μL of the base in 0.80 ml of DMSO. The reaction was rapid, as noted by the immediate disappearance of any peaks in the proton NMR spectrum from δ 4.5 to δ 7.0.

Ethyl crotonate and 2-cyclohexene-1-one were also reacted on the 0.23 mM scale. With 10 μL of base added, both reactions proceeded just as the ethyl cinnamate reaction. The typical peak changes were observed in the NMR.

Large scale without base. A colleague was successful in reacting diphenylphosphine with methylacrylate on a large scale in acetonitrile without base. The distilled product was characterized by NMR, made into a palladium complex, and submitted for elemental analysis. The results from the Midwest Microlab, Ltd. found 70.74 % C and 6.21 % H, compared with the theoretical percentages of 70.59 and 6.30.

Methyl vinyl ketone was reacted with diphenylphosphine in CDCl₃ on a 27.0 mM scale. The phosphine did not all react, so an additional 27.0 mM of the ketone was added. The 31P NMR then showed two product peaks and some unreacted phosphine. The product was not isolated, and the experiment was repeated again with base in another solvent.

Large scale in DMSO with base. Ethyl crotonate was reacted with DPP on the 20.0 mM scale in 10 ml of DMSO with 15 drops of TEAH base. The reaction proceeded quickly, and the product was isolated by vacuum distillation.
Large scale in acetonitrile with base. 3.5 ml of DPP was reacted with an excess of ethyl crotonate (3 ml) in 10 ml of acetonitrile with 15 drops of TEAH base added. The reaction flask got very warm and the solution slowly turned yellow. The reaction was followed by observing the disappearance of the P-H stretch in the IR spectrum. The product was characterized by 31-P NMR and was found to be complete after 24 hours. The solvent was stripped off in a vacuum, and the base was removed by extraction in water. The distilled product was spectrally pure with no extraneous peaks in the proton or carbon NMR.

3.0 ml of DPP was reacted with 3.0 ml of ethyl methacrylate (17.2 mM to 24.1 mM) in 10 ml of solvent and 15 drops of base. There was no color change, but the solution so hot that the solvent boiled slightly. 24 hours later, the IR showed no P-H stretch and the phosphorous NMR showed a single peak of the product. The base was removed, the solvent was stripped, and the product was distilled as before. The isolated product was pure according to proton and C-13 NMR spectra.

3.0 ml (30.9 mM) of 2-cyclohexene-1-one and 4.0 ml (23.0 mM) of DPP were reacted in 10 ml of acetonitrile with 10 drops of TEAH. The solution changed from colorless to dark yellow with the release of much heat. The reaction worked, according to the typical peak changes in the NMR. However, the product was very gummy, and it returned to the reactants during isolation and distillation.

4 ml of DPP (23.0 mM) were mixed with 15 ml of acetonitrile and 15 drops of TEAH. Methyl vinyl ketone (4.0 ml or 49.3 mM) was then added drop wise over 40 minutes. The reaction proceeded smoothly, and no attempt was made to isolate the product because of impurities in the methyl vinyl ketone. However, it did show that the reaction
works in acetonitrile and that the ketone should be distilled. Methacrolein did not work on the small scale without base. It was then reacted on the large scale in the same manner as the methyl vinyl ketone. The desired product was formed according to NMR data, but no isolation attempt was made.

Unsuccessful reactions. Phenyl vinyl sulfoxide was reacted in DMSO on the NMR tube scale. Reagents were mixed without base, and no reaction was observed. When 5 µL of base was added, some product formation was noted and the peaks were broadened. The reaction was scrapped before additional base was added.

5-norbornene-2-carboxaldehyde was reacted on a 0.23 mM scale with 5 µL of TEAH in DMSO. The reaction was unsuccessful as noted by the lack of change in the alkene peak region. Cinnamaldehyde was reacted on the small scale in CDCl₃. The NMR spectra appeared as if no alkene were added, and the reaction should be repeated. Cyclohexylidenemalononitrile and cyclopentylidenemalononitrile were reacted in CDCl₃. Results were inconclusive. All unsuccessful reactions should be repeated with base in DMSO.

Stereochemistry of addition in deuterated solvent. Ethyl crotonate was reacted with diphenylphosphine on a 0.50 mM scale in DMSO. The base used was prepared by adding sodium metal to deuterium oxide. One of the two prochiral hydrogen’s signal was diminished by 61 per cent. 2-cyclohexene-1-one was also reacted in DMSO with the Na/D₂O base. Results were inconclusive because of the close proximity of the aliphatic peaks.

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REFERENCES


