Formation of alkenes from carbonyl compounds: The Wittig Reaction.

Prof. Georg Wittig, Nobel laureate, invented one of the most important organic reactions in the 1950s, the conversion of a carbonyl compound to an alkene.

The Wittig reagent is a carbon nucleophile. Generally the reagent contains a phosphorous atom bonded to three phenyl groups and another alkyl group that has a negative charge. The nucleophile adds to the carbonyl carbon and elimination of triphenylphosphine oxide produces the alkene.

**Wittig Reaction**

![Wittig Reaction Diagram]

Important characteristics of the Wittig Reaction:

- Pure alkene of known structure
- No regioisomers of alkenes
- E/Z isomers of alkene (this could be also controlled)
- C=C double bond in the product is always exactly where the C=O group in the reactant

The Wittig reaction is an addition-elimination reaction. It involves three steps.

- Step 1 - Addition of carbon nucleophile to the carbonyl carbon
- Step 2 - Formation of oxaphosphetane
- Step 3 - Elimination of triphenylphosphine oxide and formation of the alkene
Ylide is a species that contains two oppositely charged atoms [(+ and -) charges] bonded to each other. Both atoms have octets. A Wittig reagent has no net charge. The carbon atom in Wittig reagent is nucleophilic. We can write two resonance structures for the Wittig reagents:

![Ylide resonance structures](image)

**Comparison of methods for alkene synthesis**

Let us compare dehydration of alcohols with Wittig Reaction:

\[
\begin{align*}
\text{CH}_3\text{CCH}_2\text{OH} + \text{H}_2\text{SO}_4 &\rightarrow \text{CH}_3\text{CCH}_2\text{CCH}_3 + \text{CH}_3\text{CCH}_2\text{CCH}_3 \\
\end{align*}
\]

Dehydration of alcohols gives a mixture of product alkenes:

Wittig reaction provides a single alkene product:

The position of the double bond is unambiguous in the Wittig Reaction.

**The scope of the Wittig Reaction**

A variety of alkenes can be prepared using the Wittig reaction. Both aldehydes and ketones participate in the Wittig reaction. It is possible to prepare mono, di, tri, and tetrasubstituted alkenes. Depending on the starting alkyl halide (primary or secondary only), a variety of a phosphonium salts can be prepared. The oxaphosphetane intermediate cannot be isolated generally. They eliminate phosphine oxide at low temperatures (even at -78 °C).
Major disadvantage:

One of the major disadvantages of the Wittig reaction is the formation of E and Z alkene isomers. The E/Z ratio depends on reaction conditions and the nature of the substituents on the phosphorus.

\[
\text{Acyl} + \text{R}^+\text{P}^-\text{C}_\text{R} + \text{H} \rightarrow \text{alkene}
\]

\[
\text{Mono substituted alkene}
\]

\[
\text{Disubstituted alkene}
\]

\[
\text{Trisubstituted alkene}
\]

\[
\text{Tetrasubstituted alkene}
\]

Cannizaro Reaction

Carboxylic acid derivatives undergo nucleophilic substitution, whereas aldehydes and ketones undergo nucleophilic addition.

The main reason for this difference is due to nature of the carbonyl group. The tetrahedral intermediate formed after nucleophile addition to carboxylic acid derivatives is not stable and eliminates a leaving group. The overall process is thus a nucleophilic substitution.

On the other hand, the tetrahedral intermediate formed by nucleophile addition to aldehydes and ketones is stable [lack of a leaving group] and overall process is addition. An exception to this is the Cannizaro reaction.
In this reaction, hydroxide (nucleophile) adds to benzaldehyde in the first step. After formation of the tetrahedral intermediate, a hydride (another nucleophile) adds to another molecule of benzaldehyde. After proton transfer, one obtains benzyl alcohol and benzoic acid.

Overall, one molecule of benzaldehyde is reduced to benzyl alcohol and the other is oxidized to benzoic acid.

**Conjugate Addition**

\(\alpha,\beta\)-unsaturated carbonyl compounds can react as an electrophile at two sites: the carbonyl carbon and the \(\beta\)-carbon.

\[
\begin{array}{c}
\text{H}_2\text{C} = \text{C} - \text{H} \\
\text{O} \\
\end{array}
\quad \rightleftharpoons
\quad
\begin{array}{c}
\text{H} + \text{C} = \text{H} \\
\text{+} \\
\end{array}
\quad \rightleftharpoons
\quad
\begin{array}{c}
\text{H} - \text{C} = \text{H} \\
\text{+} \\
\end{array}
\]

\(\alpha,\beta\)-Unsaturated aldehyde  \quad \text{Electrophilic at C-2}  \quad \text{Electrophilic at C-4}

Nucleophiles can attack either at C-2 or C-4. The selectivity depends on reaction conditions as well as the nucleophile itself. A variety of nucleophiles can be used for reactions with \(\alpha,\beta\)-unsaturated carbonyl compounds.

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Heteroatom nucleophiles (amines, etc) are also good for 1,4-addition.