Synthesis of Jasmonate

More resources available at www.chemistforchrist.de
**Phauson-Khand reaction: Synthesis of cyclopentenones via [2+2+1] cycloaddition**

**Net-reaction:**

R\_L + R\_S \rightarrow \text{Co}_2(\text{CO})_8 \rightarrow \text{product} \rightarrow R\_L + R\_S + \text{Co}_2(\text{CO})_8

CO comes from Co\_2(\text{CO})_8

R migh also end up here, mixtures are formed.

**Mechanism:**

1. R\_L + R\_S \rightarrow \text{Co}_2(\text{CO})_8
   - 2 CO
2. Insertion in red bond
3. Red. Elimination
4. Insertion in red bond + CO
5. To create a free coordination site


**Aldolkondensation:**

\[
\begin{align*}
 & \text{1,4 Dicarbonyl compound} \\
\end{align*}
\]
Synthesis of JASMONE

Synthesis by S. Mann  

Enamine is a too weak nucleophile.

To weak as a nucleophile?!

Solution:  
Hydrazine  

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More resources available at  
www.chemistforchrist.de
Chiral Hydrazones: Enders

Is made out of proline by reduction and protection with Mel

1. n-BuLi
2. E
3. H₃O⁺, CuSO₄

Problem: E/Z Isomers

Commercially available

Aledehyde reacts faster than the ketone!
Synthesis of JASMONE

Synthesis:

\[
\begin{align*}
&\text{1. } n-\text{BuLi} \\
&\text{2. } 3. \text{H}_2\text{O} + \text{Cu(OAc)}_2 \\
&\text{Oxidation with PCC}
\end{align*}
\]

Enolate formed at Position:

\[
\begin{align*}
&\text{1. } \text{O}_3 \\
&\text{2. } \text{Me}_2\text{S}
\end{align*}
\]

electron poor due to conjugation

Sterically hindered Base: (Kinetically controlled deprotonation)

\[
\begin{align*}
&\text{Thermodynamically controlled deprotonation}
\end{align*}
\]

What was deprotonated last will react first!

For \( E^1 \)

\[
\begin{align*}
&\text{Br} \\
&\text{CO}_2
\end{align*}
\]

For \( E^2 \)

\[
\begin{align*}
&\text{Br}
\end{align*}
\]
Synthesis of JASMONE


**Synthesis of Welch** *JOC* **1987**, *52*, 1440-1450
Synthesis of JASMONE

Additional information:

Reaction of Perkow: *JACS* 1955, 77, 2871

Perkow:

\[
\begin{align*}
\text{O} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{P(OEt)}_3 & \quad \Delta & \quad \text{O} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{P(OEt)}_2 \\
& & & & & & & & & \\
\text{O} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{P(OEt)}_3 & \quad \text{P(OEt)}_2 & \quad \text{O} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{P(OEt)}_2
\end{align*}
\]

Arbusow:

\[
\begin{align*}
\text{EtO} & \quad \text{P} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{R} & \quad \text{Br} & \quad \text{EtO} & \quad \text{P} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{R} & \quad \text{Et} & \quad \text{Br} & \quad \text{EtO} & \quad \text{P} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{R} & \quad \text{EtBr}
\end{align*}
\]

HWE-Reagent (HWE = Horner-Wadsworth-Emmons)

**Synthesis by McMurry**

*JOCS* 1973, 38, 4367-4373
*JACS* 1971, 93 5309-5311

New approach to create the 1,4 diketone

\[
\begin{align*}
\text{R} & \quad \text{O} & \quad \text{S} & \quad \text{S} & \quad \text{R} & \quad \text{NO}_2 & \quad \text{Hg(II)} & \quad \text{NaOH} & \quad \text{H}_2\text{SO}_4 & \quad \text{Nef-reaction} & \quad \text{EtOH}
\end{align*}
\]

The conditions of the Nef-reaction are rather harsh:

\[
\begin{align*}
\text{EtO} & \quad \text{P} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{R} & \quad \text{Br} & \quad \text{EtO} & \quad \text{P} & \quad \text{EtO} & \quad \text{EtO} & \quad \text{R} & \quad \text{EtBr}
\end{align*}
\]
McMurry’s attention was therefore drawn to a publication of Wildsmith, who used much milder conditions to hydrolyze an oxime (which is not that far away from a nitro group):

**Synthesis by Wildsmith** *TL* **1971, 195-198**

*Utilisation of TiCl₃ for the Nef reaction: Tetrahedron Letters, 1971, 195-198*

\[
\text{N-}OH \quad 1. \text{TiCl₃} \quad \xrightarrow{} \quad \text{NH} \quad 2. \text{H₂O} \quad \xrightarrow{} \quad \text{O}
\]

Oxime

McMurry was lucky, the reaction worked:

\[
\text{O} \quad \text{N-O} \quad \substack{\oplus \text{TiCl₃} \text{oxime} \quad \substack{\text{imine} \quad \text{O}}} \\
\text{nitro} \quad \text{N-OH} \quad \text{NH} \quad \text{O}
\]

**Synthesis:**

\[
\text{H} \quad \text{equiv} \quad \text{HO} \quad \text{Br} \quad \xrightarrow{2 \text{ eq.}} \quad \text{HO} \quad \xrightarrow{\text{Lindlar Pd}} \quad \text{HO}
\]

\[
\text{NO₂} \quad \text{NaNO₂} \quad \xrightarrow{\text{HI}} \quad \text{or:} \quad 1. \text{TiCl₃} \quad 2. \text{H₂O}
\]

\[
\text{NO₂} \quad \text{NH} \quad \xrightarrow{\text{equiv}} \quad \text{NO₂} \quad \xrightarrow{\text{TiCl₃ \quad diglyme, Δ \quad MeO \quad OMe}} \quad \text{O}
\]

\[
\text{NaOH}
\]

![Jasmone](attachment://jasmone.png)
Synthesis of JASMONE


Not a very good Electrophile due to having a quite acidic Proton in an allylic Position

That's why he decided rather to use it as a nucleophile:

That is present in a certain fraction in petrol refinery (The other compounds present in the mixture are usually hydrocarbons and do therefore not react - pure Butin is very expensive)


More resources available at [www.chemistforchrist.de](http://www.chemistforchrist.de)
Synthesis of JASMONE

PhH + cat. KCN → PhO Ph benzoine

In the presence of:

Will react much slower with CN⁻, because the Carbonyl function is stabilized by conjugation.

Stetter: Biomimetic Reaction
Tetrahedron Letters, 1974, 4505-4508

Biomimetic: Means copied from nature.

Vitamine B1 (Thiamine)

Simplified by Stetter:

Today also chiral versions for asymmetric reactions. This proton is quite acidic!

This anion replaces the role of the CN⁻ that we saw in the reaction above.
Another way to see it is:

A nucleophilic Carbene

This kind of carbenes are pretty important today:

The first carbene that was isolated, crystallized and characterized. Today there are many chiral versions available that are used in asymmetric synthesis.

Very reactive species! Prone to nucleophilic attack.

Putting different charges on the same carbon atom can also be a way of representing a carbene!

6-π Electron aromatic system, that's why the carbene is so stable!

Idea: Block the site prone to nucleophilic attack with very bulky substituents.

The 2 plane where the 2 mesityl substituents are lying in are perpendicular to each other.

The fact that carbenes can be used in catalysis as a Ligand is due to the fact that the 2 Electrons in the sp² Orbital behave like lone pair and can thus donate electron density to the corresponding metal.

Carbenes in catalysis are often named NHC-Ligands (N-Heterocyclic Carbenes) and offer many advantages compared to their Phosphorous counterparts:

a) Environmentally more friendly (often non toxic)

b) Not sensitive to oxidation

c) Lower Molecular mass, for industrial purpose this means less grams or kg of Ligand has to be added.
For adding a formyl DMF is the best reagent (Adding the Weinreb amide would more complicated).

Historically Formyl groups were added with the help of Orthoesters:

Stetter chose to change the orthoester in making one of the OEt group to a better leaving group a Phenol (OPh). This facilitates the reaction and it can be done now at r.t.


**Synthesis of Stetter**

[Diagram and reaction equations related to the synthesis of Jasmone]
Different approach using Photo-reactions:

\[
\begin{array}{c}
\text{rotation of C-C bond} \\
\text{rotation of C-C bond}
\end{array}
\]

Problem:

\[
\begin{array}{c}
\text{Biradikal} \\
\text{1,5 H-Shift}
\end{array}
\]

Only this diastereoisomer will react with HIO₄, the other cannot react in a syn-fashion.

Synthesis by Büchi \textit{JOC 1966, 31, 977-978}

Molecules with the same oxidation state:

- Imine
- Acetale
- Aminale
- Enamine
- Enole / Enole-ether

Synthesis in 3 steps

To hydrolyze a furane is not that easy because it is aromatic, but it can be done!
Synthesis of JASMONE

One step

\[ \text{n-BuLi} \rightarrow \text{Li} \]

As discussed earlier not a good E but used anyway

\[ \text{Jasmone} \]

40% (3 steps)

Problem: under the very acidic hydrolysis condition E/Z isomerization takes place! - 7% E isomer is yielded


(Electroyclic reactions)

In an electrocyclic reaction a ring is always broken or formed. Rings may, of course be formed by cycloadditions as well, but the difference with electrocyclic reactions is that just one new \( \sigma \) bond is formed (or broken) across the ends of a single conjugated \( \pi \) system.

The types of pericyclic reactions are distinguished by the number of \( \sigma \) bonds made or broken.

**Types of pericyclic reactions**

- **Cycloadditions**: 2 new \( \sigma \)-bonds are formed or broken
  \[ \Delta \sigma = \pm 2 \]

- **Sigmatropic rearrangements**: One new \( \sigma \)-bond is formed as another is broken.
  \[ \Delta \sigma = 0 \]

- **Electroyclic reactions**: One new \( \sigma \)-bond is formed or broken
  \[ \Delta \sigma = \pm 1 \]

**Rules for electrocyclic reactions**

- All electrocyclic reactions are allowed
- Thermal electrocyclic reactions involving \((4n+2)\pi\) electrons are disrotatory:
  One group rotates clockwise and one anticlockwise

- Thermal electrocyclic reactions involving \((4n)\pi\) electrons are conrotatory, in contrary reactions the two groups rotate in the same way:
  Both clockwise
  Both counterclockwise

More resources available at [www.chemistforchrist.de](http://www.chemistforchrist.de)
The Nazarov reaction:  
**Short revision**

For more details see:  
*Org. React.* 1994, 45, 1-158

In its simplest form the Nazarov cyclization is the ring closure of a doubly α,β unsaturated ketone to give a cyclopentenone.

One of the five π orbitals involved is empty, so the cyclization is a 4π electrocyclic reaction and the orbitals forming the new σ bond must interact antarafacially.

Usually the double bond is formed at the site which is higher substituted (thermodynamically more stable product) to get the double bond at the less substituted site can also be done by introducing a silicon-substituent:
Synthesis of JASMONE


The reaction proceeds through the following steps:

1. **Reagents:** HCOOH, H$_3$PO$_4$
2. **Product:**

   ![Chemical structure]

   The reaction mechanism is difficult due to tautomerization, isomerization, and elimination. For more details, consult the literature given.

**Some commercially available 5-membered rings:**

- Cyclopentane-1,3-dione
  - An important starting material for the industrial synthesis of steroids.
  - Like other 1,3 diketones in equilibrium with its enol. The Keto-Enol Tautomerization can be seen in the $^1$H-NMR.

**Examples for $E^\oplus$:**

- $R-OH$
- $EtOCl$
- $COO$

**Vinylogous Behaviour:**

- Behaves like a carboxylic acid with $pK_a = 9-10$

Synthesis of JASMONE

**Review on conjugated addition of Organocopper reagents:**

*Org. React. 1972, 19, 1-113*

*Org. React. 1992, 42, 135-631*

**Revisit on Organocopper reagents:**

**Homocuprates (Gilman reagents):** $\text{Me}_3\text{CuLi}, \text{Bu}_3\text{CuLi}$

e.g. $\text{Me}_3\text{CuLi}, \text{Bu}_3\text{CuLi}$

**Mixed homocuprate: $\text{RCuR'Li}$**

Mixed homocuprates are used in order not to waste half of the Substituent $\text{R}$:

$\text{R} = \text{MgX} + \text{CuCl}_2 \rightarrow \text{R} = \text{Cu} + \text{RCI} + \text{MgCl}$

$\text{MeCuBuLi} \text{ (Bu-Substituent is transfered), } \text{R} = \text{Cu} = \text{R'} \text{ (The R substituent is transfered, alkynes are never transferred!)}$

**Heterocuprates: $\text{RCuXR'}$**

e.g. $\cdot\text{SPh}, \cdot\text{OtBu}$ (these substituents are never transferred)

$\text{R} = \text{Li} + \text{CuSPh} \rightarrow \text{RCuSPhLi}$

**$\text{R}_2\text{CuLi}_2$ (higher order cuprates)**

Those were discovered by following experiment: MeLi and Cul were mixed in various rations and the Me-Singlet in the $^1\text{H}$-NMR was observed: When mixing MeLi and Cul in a 3:1 ratio only a single species could be seen.

**Cyanocuprates (Lipshutz cuprates) $\text{R}_2\text{CuCNLi}_2$**

$2 \text{RLi} + \text{CuCN} \rightarrow \text{R}_2\text{CuCNLi}_2 \text{ (R}_2\text{CuLi, LiCN)}$

Cyanide (CN) acts as the 3rd R group in relation to the creation of higher order cuprates.
The LiI that is created while reacting RLi and CuI is absolutely necessary for reactions to take place! The cuprates have a shape of a plane square, therefore reactions can done highly diastereoselective because cuprates are quite sensitive to sterical effects:

Example for an application of organocopper reagents: **1,4 Addition to Pyridinium-Salts**

Construction of molecules that resemble nature's NAD, NADH

**Synthesis of Grieco** *JOC, 1972, 37, 2363-2364*

Made out of:

- Heating and distillation of cyclopentadiene
- Made out of:
  - Stable
  - Not stable, reacts with itself:
Synthesis of JASMONE

For a lactone the best reducing agent to a lactole is DIBAL-H, for an ester this might not work so well!

Thermodynamically more stable due to being a trisubstituted double bond.

The textbook Clayden, Greeves, Warren and Wothers (Oxford University press, p. 951, 2004 reprint) proposes a different mechanism:

The first step is the formation of a chromate ester but this intermediate has no proton to lose, so it transfers the chromate to the other end of the allylic system where there is a proton. The chromate transfer can be drawn as a [3,3] sigmatropic rearrangement.

Very general method:

More resources available at www.chemistforchrist.de
Cope Rearrangement

Technique to enlarge cyclic systems

Synthesis of Descotes

2 steps as explained above (Grignard, Oxidation)

Simmons Smith

much cheaper

intramolecular reaction (ring closure)
Synthesis of JASMONE

\[
\begin{align*}
&\text{Br} & \text{Br} & + & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} & \xrightarrow{\text{K}_2\text{CO}_3, \text{DMF}} & (\text{CO}_2\text{Et})_2 ? \\
&\text{Br} & & & \downarrow & & & \\
&\text{Br} & \text{Br} & & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} & & (\text{CO}_2\text{Et})_2 ? \\
&\text{Br} & & & \text{CO}_2\text{Et} & \text{CO}_2\text{Et} & & \xrightarrow{\Delta, 150^\circ C} & \text{CO}_2\text{Et} ? \\
\end{align*}
\]


\[
\begin{align*}
&\text{Br} & \text{Br} & + & \text{Br}_2 (h\nu) & \text{(heat in a radical fashion)} & \rightarrow & \text{Br} & \text{Br} \text{Br} \text{Br} \\
& & & & & \text{E/Z mixture} & & \text{and..} & \\
& & & & & \text{Br} \text{Br} & & \text{Br} \text{Br} & & \text{Br} \text{Br} \\
\end{align*}
\]

The Problem is that during the radical bromination epoxides are involved due to the presence of air and one day the plant that produced Jasmone via this pathway was blown up and since then this reaction is not used industrially anymore.